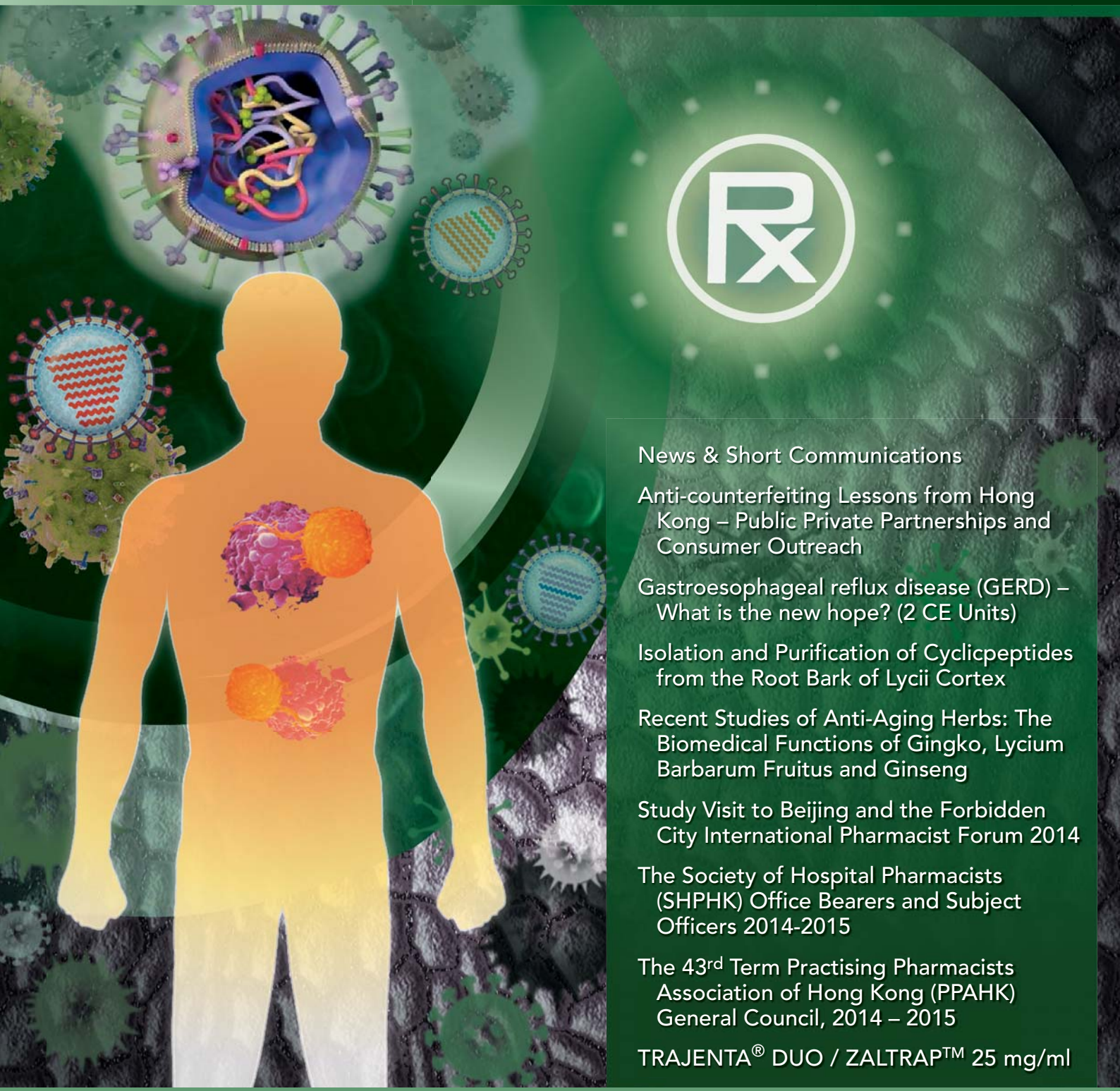
HONG KONG PHARMACEUTICAL JOURNAL

VOL 21 NO 2 Apr - Jun 2014 ISSN 1727-2874



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The Pharmaceutical Society of Hong Kong
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The Importance of Public Health Measures and Patient Education

We started to hear about the outbreak of Ebola virus disease (EVD) around March 2014 and within a few months, the epidemic that began in Guinea in December 2013, led to an epidemic in West Africa. The outbreak is caused by the Zaire ebolavirus, called simply, Ebola virus (EBOV). It has spread to Liberia, Sierra Leone, Nigeria and is the most severe outbreak of Ebola in terms of the number of human cases and fatalities since the discovery of the virus in 1976.

As of 13 August 2014, the World Health Organization (WHO) reported a total of 2,127 suspected cases and 1,145 deaths[1] (1,310 cases and 712 deaths being laboratory confirmed).[1] On 8 August, the WHO formally designated the outbreak as a public health emergency of international concern. Various aid organisations and international bodies, including the Economic Community of West African States(ECOWAS), US Centers for Disease Control and Prevention (CDC), the European Commission and China have donated funds, supplies and mobilized personnel to help counter the outbreak; charities including Médecins Sans Frontières, the Red Cross are also working in the area. In early August 2014, the U.S. Centers for Disease Control had placed staff in Guinea, Sierra Leone, Liberia, and Nigeria to assist the local Ministries of Health and WHO-led response to the outbreak.

Preventing the spread of Ebola doesn't require drugs. The traditional public health measure is to find the patients, isolate and care for them; find their contacts; educate people; and strictly follow infection control in hospitals. Basic public health measures such as isolation units and personal protective equipment to reduce direct contact with the infected are simple, inexpensive and highly effective ways to contain the spread of the disease.

It gets complicated when diseases such as Ebola germinate in poor countries where basic public health infrastructure is not established, where public health education is lacking, and where communication about the spread of the disease instills more fear about the people trying to help than about the disease itself. The result is many infected people will avoid treatment, spreading the disease and hindering the effort to contain it.

So far, there is no proven Ebola virus-specific treatment. Treatment is primarily supportive in nature and includes balancing fluids and electrolytes to counter dehydration, maintaining oxygen levels, pain management, and the use of medications to treat bacterial or fungal secondary infections. A number of experimental treatments are being studied including ZMapp and an RNA interference drug called "TKM-Ebola". Prof Tom Solomon, director of the NIHR Health Protection Research Unit in Emerging and Zoonotic infections said that ZMapp is a mixture of three monoclonal antibodies that attack proteins on the surface of the virus[2].

TKM-Ebola is developed by Tekmira Pharmaceuticals in Canada, has been tested on monkeys and in a handful of healthy human volunteers. TKM-Ebola, is designed to target strands of genetic material of the virus (RNA). The drug interrupts the genetic code of the virus and prevents it from making disease-causing proteins.[3]

The unavailability of treatments in the most affected regions has spurred controversy, with some calling for experimental drugs to be made more widely available in Africa on a humanitarian basis, and others warning that making unproven drugs widely available would be unethical. As a result of the controversy, an expert panel of the WHO endorsed the use of interventions with as-yet-unknown effects both for treatment and for prevention of Ebola, and also said that deciding which treatments should be used and how to distribute them equitably were matters that needed further discussion.[1]

The Ebola epidemic demonstrates the importance of Public Health Measures and Public Education for the prevention and spread of communicable disease. In the article on page 52, Tim K. Mackey wrote that Counterfeit medicines are an immediate patient safety threat yet their detection can be extremely difficult especially for consumers. Though patients play an important role in making safe decisions about purchasing medicines from legitimate sources, ultimately it is the responsibility of regulators, the private sector, law enforcement, public health officials and policymakers to cooperate to ensure equitable and safe access to medicines.

In the article on Gastroesophageal reflux disease (GERD) on page 55, YIP Ho Wa and CHAN Chung Ho, wrote about the inherent pharmacological and pharmacokinetic limitations of the PPI in the treatment of GERD. Novel drug development in the GI field has been aiming to tackle these limitations, bringing hope to those refractory and uncontrolled GERD cases. The novo drugs include Tenatoprazole, Alevium, Zegerid and VECAM.

With the aging population, more people are turning to herbal medicines to stay healthy. On page 65, Tsang Kwok Hong and Cheung Hon Yeung described the functions and mechanisms of Gingko, Lycium Barbarum Fruitus and Ginseng in providing anti-aging effects.

Hsu Wing Leung etal wrote about the isolation and purification of Cyclicpeptides from the Root Bark of Lycii Cortex in page 59. Lycii Cortex (LyC) is a Chinese medicine used extensively for the treatment of diabetes, lung disease, hematemesis, hypertension and inflammation. Today, more than 50 compounds have been isolated and identified in LyC. The goals of this study were to extract and isolate the peptides from the bark, to separate and purify them to a level that meets the criteria of the Hong Kong Materia Media Standards, and to confirm the structure of purified substances by the LC-MS and NMR.

Whereas public health officials must always be alert on the measures to protect public safety and to enhance patient education, scientists and researchers must continue with their search for novel compounds for treatment and prevention of diseases as well as healthy aging.

Cheng Mary Catherine
Managing Editor

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HONG KONG PHARMACEUTICAL JOURNAL

VOL 21 NO 2 Apr - Jun 2014 ISSN 1727-2874

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The Hong Kong Pharmaceutical Journal is a journal of the pharmacists, for the pharmacists and by the pharmacists. Submissions are welcome for the following sections:

- Pharmacy Education & Practice
- Drugs & Therapeutics
- OTC & Health
- Pharmaceutical Techniques & Technology
- Medication Safety
- Herbal Medicines & Nutraceuticals
- Society Activities
- New Products

Comments on any aspects of the profession are also welcome as Letter to the Editor.

There is no restriction on the length of the articles to be submitted. They can be written in English or Chinese. The Editorial Committee may make editorial changes to the articles but major amendments will be communicated with the authors prior to publishing.

It is preferable to have original articles submitted as an electronic file, in Microsoft Word, typed in Arial 9pt. Files can be sent to the following address:

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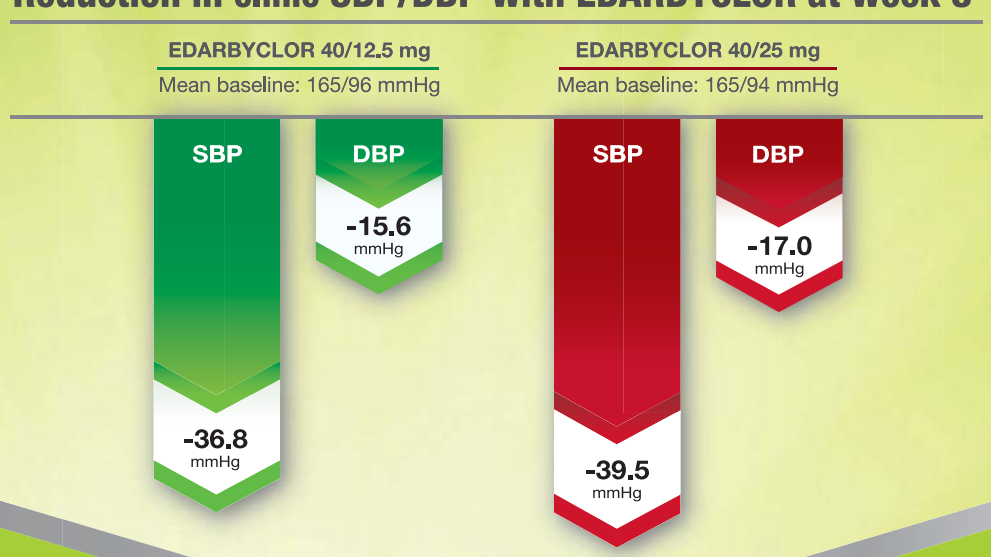
HYPERTENSION: WHEN IT IS DIFFICULT TO TREAT

Reduction in clinic SBP/DBP with EDARBYCLOR at week 8[1]



EDARBYCLOR – the first and only ARB fixed-dose combination with chlorthalidone

- **EDARBYCLOR** is the first and only ARB/chlorthalidone combination
- **EDARBYCLOR** demonstrated superior systolic BP reduction vs olmesartan HCTZ[2]
- Chlorthalidone is superior at preventing cardiovascular events compared to amlodipine besylate[3]

For detailed information, please consult full prescribing information.

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HK/JNV/EDB/21/06-2014

Prepared by Kwan Him Shek, Finna Kwok, Rico Lee, Lister Wong (Pharmacy students of the Chinese University of Hong Kong)

Singapore: Topamax (Topiramate): Updated Warnings and Precautions on Visual Field Defects

Date: April 4, 2014

Health Science Authority (HSA) announced that Janssen would like to alert healthcare professionals to the potential risk of visual field defects associated with Topamax. In double-blind, controlled monotherapy epilepsy trials, visual field defects were reported at a frequency of 0% to 1.3% in Topamax-treated adult patients. Based on cumulative data from a recent review of post-marketing safety databases and clinical trials, the package insert for Topamax will be updated in Singapore to reflect new safety information and guidance on visual field defects. Healthcare professionals are advised to consider discontinuing Topamax if visual problems occur at any time during treatment with this drug.

Source: www.drugoffice.gov.hk

Oseltamivir for Influenza in Adults and Children: Systematic Review of Clinical Study Reports and Summary of Regulatory Comments

Date: April 9, 2014

Tom Jefferson, Mark Jones, Peter Doshi, Elizabeth A Spencer, Igho Onakpoya and Carl J Heneghan have completed a review of oseltamivir for influenza in adults and children which describes its potential benefits and harms. It is a systemic review of all clinical study reports and regulatory information.

Results showed that in treatment trials on adults, oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours. There was no effect in children with asthma, but there was an effect in otherwise healthy children (mean difference 29 hours). There was no significant reduction in risk of unverified bronchitis, otitis media, sinusitis, or any complication classified as serious or that led to study withdrawal. However, Oseltamivir in the treatment of adults increased the risk of nausea and vomiting. In treatment of children, oseltamivir induced vomiting.

In prophylaxis trials, oseltamivir reduced symptomatic influenza in participants by 55% and households based on one study, but there was no significant effect on asymptomatic influenza and no evidence of a reduction in transmission. In prophylaxis studies, oseltamivir increased the risk of psychiatric adverse events during the combined "on-treatment" and "off-treatment" periods and there was a dose-response effect on psychiatric events in two "pivotal" treatment trials of oseltamivir, at 75 mg (standard dose) and 150 mg (high dose) twice daily. In prophylaxis studies, oseltamivir increased the risk of headaches on-treatment, renal events with treatment, and nausea while receiving treatment.

The evidence of clinically significant effects on complications and viral transmission is limited because of rarity of such events and problems with study design. The trade-off between benefits and harms should be borne in mind when making decisions to use oseltamivir for treatment, prophylaxis, or stockpiling.

Source: www.bmj.com

Canada: Neupogen® (filgrastim) is Associated With a Risk of Capillary Leak Syndrome in Patients with Cancer and in Healthy Donors. Neulasta® (Pegfilgrastim) is Associated with a Risk of Capillary Leak Syndrome in Patients with Cancer.

Date: April 11, 2014

Amgen Canada Inc., in consultation with Health Canada, have issued important new safety information concerning the risk of Capillary Leak Syndrome (CLS) associated with the granulocyte colony stimulating factors (G-CSF) Neupogen and Neulasta. NEUPOGEN is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-neoplastic drugs, and for the prevention and treatment of neutropenia, to maintain a normal Absolute Neutrophil Count (ANC) in bone marrow transplant patients and in patients with HIV infection. NEULASTA is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-neoplastic drugs. Cases of Capillary Leak Syndrome (CLS) have been reported in patients undergoing chemotherapy who were receiving Neupogen or Neulasta, and donors undergoing peripheral blood progenitor cell mobilization who were receiving Neupogen. CLS can cause circulatory shock and may be fatal. It is associated with hypotension, generalized edema, hypoalbuminemia and hemoconcentration. Episodes can vary in frequency and severity. Should symptoms of CLS be suspected, administration of Neupogen or Neulasta needs to be stopped and the patient closely monitored.

In Hong Kong, there are 11 registered pharmaceutical products containing filgrastim and one containing pegfilgrastim. They are prescription only medicines. Department of Health has not yet received any adverse drug reactions related to the products. In view of Health Canada's announcement, a letter to healthcare professionals will be issued to draw their attention and urge them to report any adverse drug reaction related to the drug, and the matter will be discussed in the meeting of Registration Committee of the Pharmacy and Poisons Board.

Source: www.drugoffice.gov.hk

Australia: The Use of Codeine in Children After Tonsillectomy and/or Adenoidectomy

Date: April, 2014

Health professionals are advised of the risk of rare but very serious adverse events when using codeine to treat children after tonsillectomy and/or adenoidectomy. Codeine is a widely used opioid analgesic. It can be prescribed in combination with paracetamol for children after tonsillectomy and/or adenoidectomy. However, the presence of genetic differences among patients may lead to difference in treatment response. Patients who are deficient in or lacking the enzyme that partially metabolizes codeine to morphine may not experience adequate pain relief.

On the contrary, patients who metabolize codeine to morphine very rapidly (ultra-rapid metabolisers) are at increased risk of morphine toxicity even codeine was given at low doses.

In the United States, cases of respiratory depression and death following the use of codeine in children after tonsillectomy and/or adenoidectomy have been reported. The US Food and Drug Administration (FDA) found that many of the cases of serious adverse events relating to such codeine use occurred in children with obstructive sleep apnoea. It was later identified that the affected children were ultra-rapid metabolisers of codeine. Up to 10% of Caucasians were estimated likely to be ultra-rapid metabolisers. While the estimated rate is generally lower in other ethnic groups, except for the North African and Middle Eastern people (10–29%). In Australia, the Therapeutic Goods Administration (TGA) has not received reports of death relating to codeine use in children after tonsillectomy and/or adenoidectomy. To January 2014, seven adverse events involving codeine that are suggestive of respiratory depression in children and adolescents were reported.

Health professionals are advised to use alternative analgesic for children after tonsillectomy and/or adenoidectomy if possible. If codeine is use, it should be used at the lowest effective dose for the shortest possible duration. Health professionals are also encouraged to educate parents and caregivers about possible adverse events associated with the general use of codeine in children. Parents or caregivers are advised to discontinue from using codeine and seek medical attention if any symptoms of toxicity including somnolence, difficulty in waking, confusion, shallow breathing, nausea, vomiting, constipation, lack of appetite or coma is observed in a child.

Source: www.australianprescriber.com/magazine/37/2/issue/202.pdf

FDA Questions Use of Aspirin for Primary Prevention of Heart Attack and Stroke

Date: May 2, 2014

Bayer HealthCare, LLC, requested a change in the prescribing information for health care professionals for aspirin to allow marketing of the product for prevention of heart attacks in patients with no prior history of cardiovascular disease. But the U.S. Food and Drug Administration (FDA) finds this indication questionable.

Consumers and patients who do not suffer from cardiovascular disease sometimes consider taking aspirin to reducing the possibility of having a first heart attack or stroke (primary prevention). The FDA has reviewed the available data and does not believe the evidence supports the general use of aspirin for primary prevention of a heart attack or stroke. In fact, there are serious risks associated with the use of aspirin, including increased risk of bleeding in the stomach and brain, in situations where the benefit of aspirin for primary prevention has not been established. Patients are encouraged to consult their healthcare provider if they are currently advised to take aspirin for primary prevention.

The available evidence supports the use of aspirin for preventing another heart attack or stroke in patients who have already had a heart attack or stroke, or have other evidence of coronary artery disease, such as angina or a history of a coronary bypass operation or coronary angioplasty. In such patients who have had previous cardiovascular events, the known benefits of aspirin for secondary prevention outweigh the risk of bleeding.

FDA is currently awaiting results of additional clinical trials that are underway and are estimated to have reportable results in the next few years. These clinical trials may provide new evidence that could be the basis for changing indications for aspirin.

Source: www.fda.gov

Breastfeeding and Antiepileptic Drugs

Date: May 7, 2014

The Norwegian Mother, Child Cohort Study and the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) informed women of the risks and safety issues associated with taking antiepileptic drugs (AEDs) during pregnancy and breastfeeding. The results showed that mothers with AED treatments did not cause any adverse effects to their children by breastfeeding, but prenatal exposure to AEDs would lead to psychomotor impairments of their children, especially when multiple medications are used.

The studies were conducted in breastfed and non-breastfed groups, investigating into common AEDs taken by the children of mothers: carbamazepine, lamotrigine and valproate. The results indicated that there were no differences in IQ between two groups of children, and fewer development impairments were observed at age 6 and 18 months in the breastfed group than those in the non-breastfed group. In addition, the impaired developments of children at age 36 months with prenatal AED exposure were not related to breastfeeding during the first year, as implied by the higher AED level in utero than in the mammary gland.

The Norwegian Mother and Child Cohort Study demonstrated the abnormal developments of children with fetal AED exposure were higher than those in the reference group. For instance, the impaired fine muscle movements between the study and reference groups were 25.0% and 4.8%, respectively. The NEAD study also showed that the prenatal exposure to valproate exhibited higher cognitive and behavioral impairments than other AEDs.

The studies suggested that breastfeeding should be recommended in children who have been exposed in AEDs in utero. However, more caution is advised if the mother began AED after delivery, especially for AEDs that can potentially cause damage to the immature brain of child.

Source: jama.jamanetwork.com

Canada: Health Canada Endorsed Important Safety Information on TEMODAL® (temozolomide)

Date: May 7, 2014

Merck Canada Inc., in consultation with Health Canada, inform health care professional regarding the important safety information about TEMODAL® (temozolomide), an antineoplastic agent indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment and indicated for treatment of adult patients with glioblastoma multiforme or anaplastic astrocytoma and documented evidence of recurrence or progression after standard therapy.
Cases of hepatic injury, including fatal hepatic failure, have been reported in patients receiving temozolomide. Liver toxicity may occur several weeks after initiation of treatment or after temozolomide discontinuation.

It is advised that liver function tests should be performed prior to treatment initiation; after each treatment cycle and midway during the treatment cycle for patients on a 42 day treatment cycle. For patients with significant liver function abnormalities, the benefits and risks of continuing treatment should be carefully considered.

The Temodal® (temozolomide) Product Monograph has been revised to include updated information on the risk of hepatic injury and specific recommendations for monitoring of liver function.

Source: www.healthycanadians.gc.ca

US: Pradaxa (Dabigatran): Drug Safety Communication - Lower Risk for Stroke and Death, but Higher Risk for GI Bleeding Compared to Warfarin

Date: May 14, 2014

Based on a much larger and older patient population and a more sophisticated analytical method to capture and analyze the events of concern, the U.S. Food and Drug Administration (FDA) recently completed a new study in Medicare patients comparing the anticoagulant Pradaxa to warfarin, for risk of ischemic or clot-related stroke, bleeding in the brain, major gastrointestinal (GI) bleeding, myocardial infarction (MI), and death. The new study included information from more than 134,000 Medicare patients, 65 years or older, and found that among new users of blood-thinning drugs, Pradaxa was associated with a lower risk of clot-related strokes, bleeding in the brain, and death, than warfarin. The study also found an increased risk of major gastrointestinal bleeding with use of Pradaxa as compared to warfarin. The MI risk was similar for the two drugs.

Since stopping the use of blood-thinning medications such as Pradaxa and warfarin can increase the risk of stroke and lead to permanent disability and death, healthcare professionals who prescribe Pradaxa should continue to follow the dosing recommendations in the drug label.

Source: www.drugoffice.gov.hk

UK: The Benefits and Risks of Statins

Date: May 17, 2014

Medicines and Healthcare products Regulatory Agency (MHRA) published its position on the benefits and risks of statins, following the recent media coverage about side effects associated with them.

MHRA advised that people should continue to take their statins as prescribed. Large clinical trials have shown that statins can save lives by reducing the risk of heart attacks, strokes and the need for heart surgery. The benefits of taking statins strongly outweigh any risks. However like all medicines, statins can cause side effects in some people. Most side effects experienced by people who take statins are mild and product information lists advice on how to use statins and any potential side effects. If patients have any concerns about their medicines then they should speak to their doctor.

Source: www.drugoffice.gov.hk

US: Revolution to a New Standard Treatment of Diabetic Macular Edema

Date: June 11, 2014

The National Institutes of Health-sponsored Diabetic Retinopathy Clinical Research Network (DRCR.net) announced a novel treatment of diabetic macular edema (DME), a visual disorder that swells the central region of the macula by the formation of hard educates. This effective treatment was accomplished by the combination of ranibizumab and laser photocoagulation.

The conventional treatment is to monitor blood pressure and daily diet. In addition, a laser photocoagulation has been used to improve the vision of patients with DME since mid-1980s, but 15% of the patients have no improvement regardless of this treatment. In 2001, intravitreal injections of corticosteroids were introduced for DME treatment. However, these treatments were rejected because of adverse effects such as glaucoma and cataract. In 2006, investigators discovered DME was caused by vascular endothelial growth factor (VEGF), and subsequently ranibizumab, an FDA-approved anti-VEGF drug, was developed as an intravitreal injection for DME treatment.

Recent study demonstrated that the combination of ranibizumab and laser photocoagulation performed an effective treatment of DME. For example, 49% of patients showed obvious visual improvement compared with 36% of those who were treated with laser only. The risk of vision loss between the combination treatment and laser group were 3% and 13%, respectively. Furthermore, the new treatment could maintain their visual acuity for 3 years with no serious adverse effects. The DRCR.net is further investigating any better medications and methods that can prevent the cause and deterioration of DME. They are also investigating possible drug delivery systems that can provide effective administration and examination of patients with DME.

Source: jama.jamanetwork.com

Canada: Health Canada Endorsed Important Safety Information on Intravenous ZOFRAN (Ondansetron Hydrochloride Dihydrate)

Date: June 12, 2014

GlaxoSmithKline Inc., in consultation with Health Canada, inform health care professional regarding the important new safety information about the dosing and administration of *intravenous (IV)* ondansetron (ZOFRAN®), which is indicated for the prevention of nausea and vomiting associated with emetogenic chemotherapy, including high dose cisplatin, and radiotherapy in geriatrics (>65 years of age).

Healthcare professionals should use the new dosage and administration recommendations to mitigate the risk of QT prolongation in elderly patients. The dosing restrictions for geriatrics are summarized as follow: in patients ≥75 years of age, the initial IV dose must not exceed 8 mg. While in patients <75 years of age, the initial IV dose must not exceed 16 mg. Subsequent IV doses must not exceed 8 mg and may be given 4 and 8 hours after the initial dose. All IV doses must be diluted in 50–100 mL of saline or other compatible fluid. Moreover, all IV doses must be infused over no less than 15 minutes. However, there are no changes to the recommended oral dosing.

The risk of dose dependent QT interval prolongation, which can lead to Torsade de Pointes (TdP), a potentially life-threatening heart arrhythmia, is expected to be greater with faster rate of infusion and larger doses for the ondansetron IV administration. Caution must be used if administering ondansetron to patients with risk factors for QT interval prolongation or cardiac arrhythmias and electrolyte imbalances should be corrected prior to ondansetron administration.

The Dosage and Administration section of the ZOFRAN® Product Monograph has been updated with the new safety information.

Source: www.healthycanadians.gc.ca

US / EU: Adding General Warning to Testosterone Products about Potential for Venous Blood Clots

Date: June 20, 2014

The U.S. Food and Drug Administration (FDA) is requiring manufacturers to include a general warning in the drug labeling of all approved testosterone products about the risk of blood clots in the veins. Blood clots in the veins, also known as venous thromboembolism (VTE), include deep vein thrombosis (DVT) and pulmonary embolism (PE). The risk of venous blood clots is already included in the labeling of testosterone products as a possible consequence of polycythemia, an abnormal increase in the number of red blood cells that sometimes occurs with testosterone treatment. In addition, there have been post-market reports of venous blood clots unrelated to polycythemia, so FDA is requiring a change to drug labeling of all testosterone products to provide a more general warning regarding venous blood clots and to ensure this risk is described consistently in the labeling of all approved testosterone products.

Source: www.fda.gov

US: FDA Warns that Cancer Drug Docetaxel may cause Symptoms of Alcohol Intoxication after Treatment

Date: June 20, 2014

The U.S. Food and Drug Administration (FDA) warned health care professionals of the intoxication during and after treatment caused by the intravenous chemotherapy drug docetaxel as it contains ethanol. When prescribing or administrating the drug, health care professionals are advised to take the alcohol content into consideration, particularly in those whom alcohol intake should be avoided or minimized and when using it in conjunction with other medications.

Patients should be aware that the drug may cause them to feel drunk so they should avoid driving, operating machinery, or performing other activities that are dangerous for one to two hours after the infusion. Also, there might be interactions between the alcohol in docetaxel and some medications such as pain relievers and sleep aids to worsen the intoxicating effects.

The prescription chemotherapy drug docetaxel is used to treat several cancers including cancers of the breast, prostate, stomach, head and neck cancers, and non-small-cell lung cancer. The brand-name products Taxotere, Docefrez, and Docetaxel Injection and generics are currently marketed. Different products of docetaxel vary in alcohol content that is needed to dissolve the active ingredients so it can be given intravenously (see Docetaxel Formulations and Alcohol Content). Health care professionals should pay attention to the differences in formulations so as to monitor and counsel patients appropriately.

Source: www.fda.gov

The United States: Over-The-Counter Topical Acne Products - Rare But Serious Hypersensitivity Reactions

Date: June 26, 2014

FDA is warning that certain over-the-counter (OTC) topical acne products can cause rare but serious and potentially life threatening allergic reactions or severe irritation. Consumers should stop using their topical acne product and seek emergency medical attention immediately if they experience hypersensitivity reactions such as throat tightness; difficulty breathing; feeling faint; or swelling of the eyes, face, lips, or tongue. Consumers should also stop using the product if they develop hives or itching. The hypersensitivity reactions may occur within minutes to a day or longer after product use. These serious hypersensitivity reactions differ from the local skin irritation that may occur at the product application site, such as redness, burning, dryness, itching, peeling, or slight swelling, that are already included in the Drug Facts labels.

Based on the information reported to FDA, it cannot be determined if the serious hypersensitivity reactions were triggered by the acne products' active ingredients, benzoyl peroxide or salicylic acid, the inactive ingredients, or by a combination of both. FDA is continuing to monitor and evaluate this safety issue, and will work with manufacturers regarding any future label changes that would address the risk of severe hypersensitivity reactions. Consumers are advised that before using an OTC topical acne drug product for the first time, apply a small amount to one or two small affected areas for 3 days to make sure no hypersensitivity symptoms will develop.

Source: www.fda.gov

US: FDA Recommends not Using Lidocaine to Treat Teething Pain and Requires New Boxed Warning

Date: June 26, 2014

The U.S. Food and Drug Administration (FDA) would like to warn that prescription oral viscous lidocaine 2 percent solution should not be used to treat infants and children with teething pain. When used in infants and young children, it can cause serious or even life-threatening adverse effect. In order to highlight this information, the FDA is requiring a new Boxed Warning, FDA's strongest warning, to be added to the drug label.

In 2014, 22 case reports of serious adverse reactions, including death, in infants and young children who were given oral viscous lidocaine 2 percent solution were reviewed by FDA. These infants and young children 5 months to 3.5 years of age were given lidocaine solution for treatment of mouth pain, including teething and stomatitis and some of them ingested the solution accidentally. Health care professionals are reminded that oral viscous lidocaine solution should not be prescribed to treat teething pain. Parents and caregivers are advised to follow the American Academy of Pediatrics' recommendations for treating teething pain.

1. Use a teething ring chilled in the refrigerator (not frozen).
2. Gently rub or massage the child's gums with your finger to relieve the symptoms.

Rubbing topical pain relievers and medications on the gums are not necessary or even useful because they wash out of the baby's mouth within minutes. Seizures, severe brain injury, and problems with the heart can be resulted when too much viscous lidocaine is given to infants and young children or they accidentally consume too much. Cases of overdose due to wrong dosing or accidental ingestion have resulted in infants and children being hospitalized or dying.

In addition to the *Boxed Warning*, FDA feels the necessity for revising the *Warnings* and *Dosage* and *Administration* sections of the drug label to include description of the risk of severe adverse events and additional instructions for dosing when the drug is prescribed for approved uses. Meanwhile, FDA encourages parents and caregivers not to use topical medications for teething pain purchased over the counter as some of them can have undesirable effects. For example, in 2011, the FDA warned that using OTC benzocaine gels for teething or mouth pain can cause a rare but life-threatening condition called methemoglobinemia.

Source: www.fda.gov

The Pharmacy & Poisons (Amendment) Bill 2014

Date: July 17, 2014

The Pharmacy and Poisons (Amendment) Bill 2014 was gazetted on 21 March 2014. The main purpose of the Bill is to implement certain recommendations in the Report of the Review Committee on the Regulation of Pharmaceutical Products in Hong Kong published by the Food and Health Bureau in December 2009. In addition, the FHB also took the opportunity to tidy up some outdated sections and revised certain provisions of the laws including the definitions of "Authorized Sellers of Poisons" and "Pharmaceutical Products".

The LegCo Bills Committee invited stakeholders for a debutation on 20 May 2014. About 20 organizations and individuals attended to give their views on the Amendment Bill. The views were broadly summarized as follows:

(a) Requested to establish a separate statutory body to take over the existing function of the Pharmacy and Poisons Board for regulating registered pharmacists;

(b) Requested to include more representatives from the industry as members of the Board, so that the Codes of Practice/Code of Conduct issued by the Board for various licensed and listed traders as well as registered pharmacists will be more representative;

(c) Expressed concerns towards the proposal which allows a person, who is not a registered pharmacist, to become an authorized person if he/she hollds a qualification awardes on completion of a course recognized by the Board;

(d) Expressed concern towards the proposed amendments to the definition of "authorized seller of poisons";

(e) Expressed concern towards the proposed amendments to the definition of "pharmaceutical product" and "medicine";

(f) Opposed to the proposal of extending the validity of clinical trial certificates and medicinal test certificates from two years to five years; and

(g) Expressed concerns towards the proposed requirement of placing orders of pharmaceutical products in written form.

The Bills Committee had held meetings to discuss on the Bill for this LegCo year on 24/4, 20/5, 10/6, 17/6, 4/7 and 17/7/14. It is now summer recess and the Bills Committee meeting will start again in September/ October 2014.

Source: http://www.legco.gov.hk/yr13-14/english/bc/bc54/papers/bc54_c.htm

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Integrated Safety Information: CONTRAINDICATIONS: Avamys Nasal Spray is contra-indicated in patients with hypersensitivity to any of the ingredients. **WARNINGS AND PRECAUTIONS:** - undergoes extensive first-pass metabolism by the liver enzyme CYP3A4, therefore the pharmacokinetics of intranasal fluticasone furoate in patients with severe liver disease may be altered. Based on data with another glucocorticoid metabolised by CYP3A4, co-administration with ritonavir is not recommended because of the potential risk of increased systemic exposure to fluticasone furoate. Systemic effects with nasal corticosteroids have been reported, particularly at high doses prescribed for prolonged periods. The following adverse events have been reported with a frequency of ≥1/100 to 1/10 (common) and ≥1/10 (very common) **CLINICAL TRIALS DATA:** Very common: Epistaxis; Common: Nasal ulceration **POST-MARKETING DATA:** Common: Headache Please refer to the full prescribing information for further information and prior to administration.

AVAMYS™ NASAL SPRAY Abbreviated Prescribing Information: INDICATIONS AVAMYS is indicated for the treatment of the symptoms of seasonal and perennial allergic rhinitis in patients 2 years of age and older. **DOSAGE AND ADMINISTRATION** Administer AVAMYS (27.5mcg/spray) by the intranasal route only. Adults & adolescents ≥12 years: The recommended starting dosage is 110mcg (2 sprays in each nostril) once daily. When the symptoms have been controlled, reducing the dosage to 55mcg (1 spray in each nostril) once daily may be effective for maintainence. Children 2-11 years: The recommended starting dosage in children is 55mcg (1 spray in each nostril) once daily. Children not adequately responding to 55mcg may use 110mcg (2 sprays in each nostril) once daily. Once symptoms have been controlled, the dosage may be decreased to 55mcg once daily. **CONTRAINDICATIONS** Hypersensitivity to any of the ingredients. **WARNINGS AND PRECAUTIONS** AVAMYS undergoes extensive first-pass metabolism by CYP3A4, therefore the pharmacokinetics of AVAMYS in patients with severe liver disease may be altered. Co-administration with ritonavir is not recommended. **INTERACTIONS** In a drug interaction study of AVAMYS with the potent CYP3A4 inhibitor ketoconazole there were more subjects with measurable AVAMYS plasma concentrations in the ketoconazole group compared to placebo. The enzyme induction and inhibition data suggest that there is no theoretical basis for anticipating metabolic interactions between AVAMYS and the cytochrome P450-mediated metabolism of other compounds at clinically relevant intranasal doses. Therefore, no clinical studies have been conducted to investigate interactions of AVAMYS on other drugs. **PREGNANCY AND LACTATION** Adequate data are not available regarding the use of AVAMYS during pregnancy and lactation in humans. AVAMYS should be used in pregnancy only if the benefits to the mother outweigh the potential risks to the foetus. Following intranasal administration of AVAMYS at the maximum recommended human dose (110mcg/day), plasma AVAMYS concentrations were typically non-quantifiable and therefore potential for reproductive toxicity is expected to be very low. **ADVERSE REACTIONS** Epistaxis, nasal ulcerations. Hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria. Headache. Rhinalgia, nasal discomfort (including nasal burning, nasal irritation and nasal soreness), nasal dryness. **OVERDOSE** Acute overdose is unlikely to require any therapy other than observation. Abridged PI (GDS 07/IPI06)

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Indication
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Composition
Per 5ml sachet containing 1 gram of sucralfate gel

Product mechanism and features
Not offered by any Proton Pump Inhibitors, H2-blockers or other acid suppressing agents, Sucrate Gel uniquely forms a cyto-protective layer on the inflamed and damaged mucosae of the G.I. tract. This layer prevents stomach acid, pepsin and bile salts from further eroding the ulcerated tissues. Also, Sucrate Gel stimulates the production of endogenous tissue growth factors (epidermal growth factor, fibroblast growth factor, transforming growth factor alpha, platelet derived growth factor), which promote cell regeneration and angiogenesis.

Active ulcer healing is achieved through better reconstruction of mucosal architecture and thus prevents early relapse.

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Dosage
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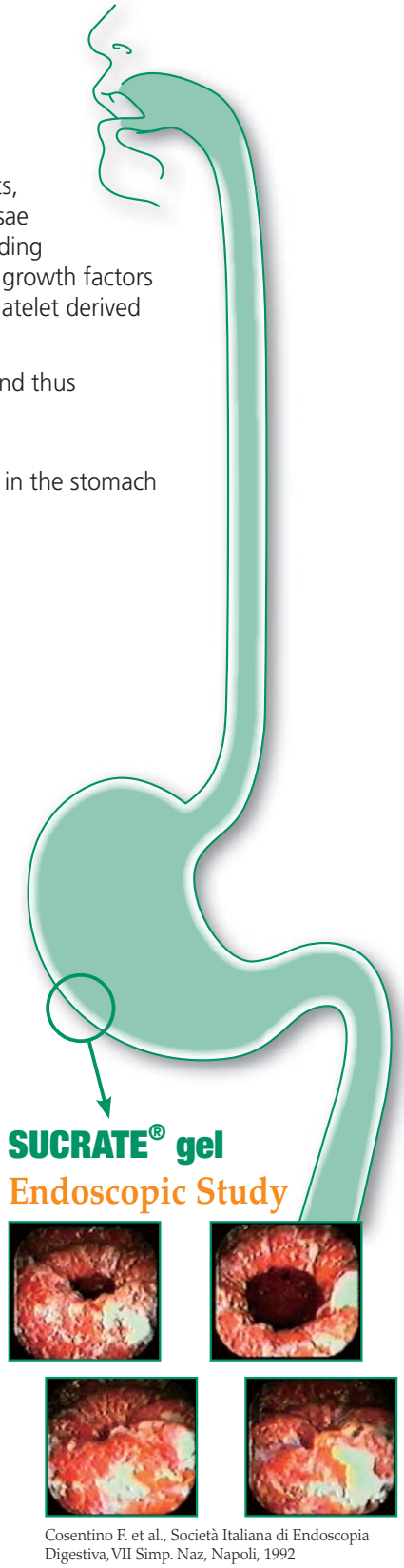

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Anti-counterfeiting Lessons from Hong Kong – Public Private Partnerships and Consumer Outreach

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INTRODUCTION

Tim K. Mackey, MAS, PhD holds a Masters degree in Health Law & Policy and a PhD in Global Public Health. He has been working on the issue of counterfeit medicines for close to a decade, and recently, in September 2013, met with Hong Kong and Macau stakeholders to discuss their efforts in this area.


Dr. Tim K. Mackey

Though a true solution to this illicit parallel global drug supply chain requires cooperation and coordination amongst all relevant global stakeholders, national and local initiatives that are tailored to the unique risk factors of their communities can provide important lessons on how to implement successful partnerships and solutions. As one of the largest trading hubs in the world, Hong Kong represents a potential consumer and import/export market for counterfeit medicines and hence, efforts by Hong Kong stakeholders attempting to address the issue are relevant to the global community and should be further explored and assessed.

BACKGROUND

The global illicit trade in fake, falsified, fraudulent, substandard, and/or as they are commonly referred to "counterfeit" medicines is an enormous global public health problem that spans virtually all countries and impacts all types of healthcare settings. The World Health Organization (WHO) has estimated that greater than 10-30% of medicines are counterfeit in least developed countries and low-middle income countries.[1] Prevalence of counterfeits in higher income markets is not well known, but even in the United States of America, a highly regulated and controlled drug supply chain, counterfeit medicines have infiltrated clinical practice and adversely impacted patients.[2] Because of the severity of this issue, a number of stakeholders, including those in the private sector, international organizations, national drug regulatory agencies, law enforcement, customs officials, clinicians, pharmacists, and members of civil society, have been working on various anti-counterfeiting strategies and enforcement actions.[1]

Central to the trade in counterfeit medicines is the involvement of pharmaceutical crime syndicates engaged in diversion/theft of pharmaceuticals, large-scale counterfeiting/illicit manufacturing, and illegal online drug sales. These criminal actors leverage globalized trading systems and technology solutions to distribute dangerous drugs worldwide often with a high degree of anonymity and low risk compared to other criminal activities such as the trade in illicit drugs. International organizations such as the WHO, UN Office of Drugs and Crime, Interpol, and the World Customs Organization have attempted to address the multifaceted aspects of this trade, but have been limited in their effectiveness.[3]

IMPACT ON CONSUMERS

Counterfeit medicines are an immediate patient safety threat yet their detection can be extremely difficult especially for consumers. Often packaging, actual product, and even security features can be reproduced to a high degree of accuracy by counterfeit medicine producers who are more concerned for the appearance of authenticity than the quality of the medicine itself.[4] In fact, counterfeit sellers may even utilize authentic packaging that is either purchased or procured from pharmaceutical waste sources. In addition, even if a drug is suspected to be counterfeit, testing of the product to confirm its status is largely inaccessible and costly. This makes it difficult for patients to both detect and report suspected counterfeit medicines especially in non-clinical settings where a licensed pharmacist may not be available for consultation.

Most importantly, however, there have been documented patient deaths associated with counterfeit medicine consumption. This includes a high prevalence of counterfeit anti-malarial drugs detected in Southeast Asia (potentially leading to anti-microbial resistance), substandard hepatitis B and rabies vaccine that has reportedly killed or sickened children in mainland China, surveys that have shown an estimated 30% of drugs sold in Kenya are fake, and deaths from illicit online drug sales in the United States and Canada.[3] Though the true scope and severity of the problem is not well known, it is clear that patients throughout the world have been impacted by this growing public health crisis.

Alarmingly, counterfeit medicines often also impact the most vulnerable patient populations, including those who lack

access to healthcare services, those who are poor and require lower prices to purchase medicines that may lack legitimacy, and those who lack sufficient health literacy. For these populations, buying a counterfeit drug can result in severe social and economic damage including loss of sustenance income, injury/disability, poorer health or even death that can have a tremendous negative impact in their families and communities.

Unfortunately, patients are the clear victims of the global counterfeit medicines trade, even though they may often be acutely unaware of the potential threat of these medicines. Though patients play an important role in making safe decisions about purchasing medicines from legitimate sources, ultimately it is the responsibility of regulators, the private sector, law enforcement, public health officials and policymakers to cooperate to ensure equitable and safe access to medicines.

ENGAGEMENT WITH THE PHARMACEUTICAL INDUSTRY

The pharmaceutical industry plays a crucial role in addressing the global criminal trade in counterfeit medicines. Specifically, the pharmaceutical industry's participation is indispensable in providing necessary technical assistance and resources to engage in detection, testing, and aiding law enforcement and customs officials in their investigations.

Several pharmaceutical manufacturers have been actively engaged in the fight against counterfeit medicines and operate security programs to purchase and sample medicines in high-risk areas. They often work with a local law enforcement or customs counterpart to facilitate these types of investigations that can then form the basis of evidence needed for the law enforcement and justice system to pursue possible criminal prosecution.

ROLE OF PHARMACISTS IN PATIENT SAFETY AND PHARMACOVIGILANCE

While various types of health care professionals are potentially impacted by counterfeit medicines in their practice, arguably none is more important or more crucial in protecting patient safety than the pharmacist. Pharmacists play an important role in dispensing medications and educating patients about their drugs. Hence, they can represent the front line in the fight against these fake medicines if actively engaged and partnered with.

As other healthcare professionals may not have the requisite knowledge-base to know when a medicine is a possible counterfeit product, pharmacists can act as an informed intermediary that can both notify clinicians and patients about suspected problems. These include risk factors such as "no prescription" marketing of drugs in those jurisdictions/therapeutic classes that clearly require a prescription and supervised dispensing, medicines where the price is extremely cheap compared to other similar products, those where the sourcing of the product is suspect (i.e. Internet sales or from an unknown distributor/manufacturer), and instances where drugs are sold under other questionable circumstances.

In many cases, the pharmacists may represent the best source for detecting counterfeit medicines in the healthcare delivery system model. They can also serve a dual-role of actively engaging in surveillance and educating clinicians and patients on the serious health risks associated with these dangerous drugs.

PUBLIC-PRIVATE PARTNERSHIPS

A relatively successful governance mechanism to mobilize cooperation and coordination of various stakeholders against counterfeit medicines has been the formation of public-private partnerships (PPPs). PPPs come in many forms but largely consist of active engagement and partnership between the public and private sector for particular issues of common interests and shared goals.

In the case of counterfeit medicines, global PPPs, such as the Partnership for Safe Medicines represents a first step in more broader stakeholder engagement and expansion of these efforts to local partnerships.[4,5] Other PPPs such as the WHO's International Medical Products Anti-Counterfeiting Taskforce (IMPACT) also showed early signs of success, but has had its operations largely discontinued due to disagreement among member states on how to address conflict between public health and commercial interests.[3]

NATIONAL COUNTERFEIT MEDICINES POLICY MAKING

Despite current efforts, there is also a clear need to enact national legislation specific to the counterfeit medicines trade and strengthen penalties and law enforcement efforts.[6] Crucial to this health policy design is the need for legislation that: (a) appropriately provides a legal definition for what constitutes a "counterfeit" medicine (for example differentiating counterfeits from medicines *unintentionally* made substandard by an authorized manufacturer); (b) strengthens both civil and criminal penalties to effectively deter this lucrative trade; (c) leverages existing laws and regulations (i.e. customs laws, etc.) to strengthen the legislation; (d) includes funding and training for anti-counterfeit activities including education of healthcare professionals, customs agents, prosecutors, judges, and the public; and (e) includes regular surveillance and testing operations to detect and enforce against counterfeit medicine purveyors.

LESSONS FROM HONG KONG AND MACAU

Efforts by Hong Kong and Macau stakeholders can provide important lessons to the global community regarding implementation of solutions to prevent counterfeit medicine sale and distribution. Because of its strategic business location in East Asia, its free trade policy, and its close proximity and business ties to China where a high degree of counterfeit medicines have been detected as manufactured, Hong Kong represents a global transshipment location for counterfeit drugs with a clear global impact. In addition, counterfeit medicines intended for shipment through Hong Kong to other countries

may also "spill over" into the local market or questionable providers may simply source them from China for local sale. Because of these unique challenges, tailored solutions are required and provide interesting case studies for examination.

One interesting aspect of Hong Kong's anti-counterfeiting efforts has been its use of an informal PPP mechanism to mobilize action. This includes active participation between the HK Customs and Excise Department (C&E), the HKSAR Department of Health, the Hong Kong Association of the Pharmaceutical Industry (HKAPI), the Consumer Council, and the HK General Chamber of Pharmacies. Through this participation, this group of stakeholders that does not operate under a formalized framework, is able to leverage resources, effectively coordinate largely free of extensive bureaucratic processes, and maintain representation from key areas of public health, customs and enforcement, the pharmaceutical industry, consumer advocates, and pharmacists professionals.

Also, Hong Kong partnership initiatives aimed at counterfeit drug surveillance, increasing reporting and prosecutions, and engaging in consumer education and outreach, are unique tools that have been implemented to address this multifaceted problem. These include regular counterfeit surveillance and sampling of pharmacy establishments, HKAPI and C&E operation of a toll free hotline and reward scheme for tips leading to seizure and conviction (up to HK$10,000), publishing a database of authentic drugs for comparison purposes, and the Consumer Council's CHOICE magazine publication of offending establishments that have been identified as engaged in counterfeit drugs sales.

Similarly, the Macau government through the Macao SAR Consumer Council has also engaged in initiatives aimed at preventing the sale of counterfeit medicines within their own local context. This includes developing a "Code of Practice" for drugstores and "Certified Shop" emblem that specifically requires authenticity and quality of medicines.

Collectively these multisectoral initiatives offer possible localized solutions that could be extended to other communities, countries, regions and even incorporated into global health governance efforts aimed at combating counterfeit medicines. In order to increase their appeal, these programs should actively engage in program evaluation and monitoring and evaluation and publicly disseminate results on experienced challenges and successes so others can further assess them for possible adoption.

CONCLUSION

Efforts by Hong Kong and Macau stakeholders provide important lessons on how anti-counterfeit medicines initiatives can involve successful partnerships and localized solutions. Though not all these solutions may be applicable to the overall global trade in counterfeit medicines, they may represent important case studies necessary to engage patients, healthcare providers, pharmacists, regulators and policymakers on the dangers of counterfeit medicines and the need for collective action.

ACKNOWLEDGMENTS

I would like to thank the United States Department of State, Bureau of International Information Programs as well as the Consulate General of the United States Hong Kong & Macau for their support through the U.S. Speaker and Specialist Grant.

Author's background

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Gastroesophageal reflux disease (GERD) – What is the new hope?

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ABSTRACT

Gastroesophageal reflux disease (GERD) is a disease which often does not catch immediate attention from the patients. Proton-pump inhibitor (PPI) is a class of drugs that is effective to relief the symptoms but there are still a portion of patients suffering from the disease despite regular administration after a period of time. PPI has its limitations, and sometimes lead to treatment failure. On the other hand, technology allows newly developed compounds to help those refractory cases. So what is the new hope to those patients?

Keywords: *Gastroesophageal reflux disease (GERD), Proton-pump inhibitor (PPI), refractory, novel drugs*

INTRODUCTION

Gastroesophageal reflux disease (GERD) describes broadly a spectrum of acid reflux diseases, from as minor as non-cardiac heartburn to as severe as Barrett's esophagus. It has been a prevalent disease in Western countries, but is gaining increasing attention in Asian region, with a growing prevalence in Asia.[1] A large study[2] in 2002 involving 16,606 subjects showed that 3.8% of study subjects had reflux esophagitis in Hong Kong and it is now estimated around 10% of the population suffer from the disease. The mainstay of pharmacotherapy is the acid-suppressive medications, most notably proton pump inhibitors (PPIs), with or without the addition of pro-motility medications, mucosal protectants and/or antacids.

Even though PPIs are highly effective in acid suppression, a once-daily regimen for 4-8 weeks can only achieve up to 85% of sufficient symptoms relief and tissue healing.[3] The remaining 15% may need to have a twice-daily dosing regimen after initial failure of treatment.[3] 'Twice-daily' is not a licensed frequency for all available PPIs in the market, but it is recommended by the 2008 American Gastroenterological Association guidelines for GERD for patients with an esophageal syndrome with an inadequate symptom response to once-daily PPI therapy.[4] On the other hand, 80% of the initially relieved patients will experience disease recurrence within 6 months after discontinuation of PPI therapy.[3] And some patients on once-daily or even twice-daily PPI for GERD will still experience breakthrough symptoms and nocturnal symptoms. These patients with 'refractory GERD' may be exposed to risks of complications. Considering these unmet needs, there is renewed interest in medical strategies for GERD. So, what is the new hope?

PROTON PUMP INHIBITORS[3, 5, 6, 7]

Various guidelines and references have been advocating the first-line usage of oral PPIs in the management of GERD. For a short recap, PPIs are weak-base prodrugs and will be converted to their active forms after absorption. In order to protect the acid-labile prodrugs from the acidic environment of the stomach, the drugs are often formulated as a acid-resistant dosage form (enteric coated or delayed-release formulation). Once the drugs are absorbed, they accumulate in the acidic canalicular space of the active parietal cells (site of action), where the pH is less than 2.0. At this pH, they are converted to the active forms of the drugs, which then exert their acid-suppressive effect by forming a covalent bonding with the 'activated' H/K-ATPase, which is the last step of acid secretion *(please refer to figure).* Because of this covalent binding of PPIs to the proton pumps of the parietal cell, the duration of action (1-2 days for synthesis of new H/K-ATPase pump molecules), i.e. inhibition of acid secretion, is much longer than their plasma elimination half-lives (1-2 hours). However, both accumulation and activation of the drug require the presence of acid secretion. Up to 3-4 days of daily administration of the drugs are required to reach the full acid-inhibiting ability because pumps that are non-secreting will not be inhibited. Table 1 briefly summarizes some important information of the PPIs available.

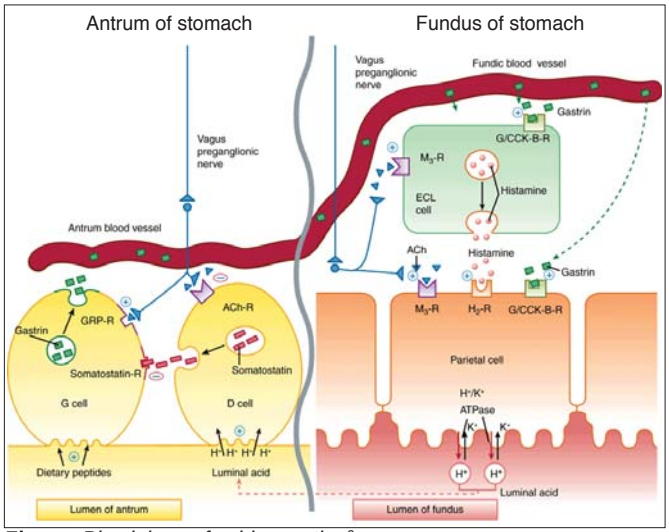

Figure: *Physiology of acid secretion*[3]

Table 1: Summary of the available proton-pump inhibitors[15, 16]

	Usual Dosage in GERD	Dosage adjustment in renal impairment	Dosage adjustment in hepatic Impairment	Time of administration	Ryle's Tubing or Swallowing Problem
Ompeprazole (Losec)	20-40mg daily	Not required	Consider to reduce the dosage to 10-20mg daily for impaired hepatic function	In morning without food	Water dispersible^
Lansoprazole *(Takepron OD)*	15-30mg daily	Not required	Consider dosage adjustment in severe hepatic impairment, no specific dosage recommendation	Before meal	Water dispersible#
Pantoprazole *(Pantoloc)*	20-40mg daily	Not required	Maximum 20mg in severe hepatic impairment. Discontinuation of treatment should be considered for patients with further deterioration of liver function	One hour before meal	**Not suitable**
Esomeprazole (***Nexium***)	20-40mg daily	Not required	Maximum 20mg in severe hepatic impairment	Not specified@	Water dispersible#
Rabeprazole *(Pariet)*	10-20mg daily	Not required	Use with caution in patients with severe hepatic impairment.	Not specified	Not suitable
Dexlansoprazole *(Dexilant)*	30-60mg daily	Not required	Consider 30mg daily for moderate hepatic impairment Child-Pugh Class B)	With or without food	Allowable+

^ *LOSEC MUPS allows dispersion of the tablet in non-carbonated water. The dispersion has to be administered within 30 minutes. Ingest without chewing the enteric-coated pellets.*
@ *The instruction of one hour before meal administration is included in the US prescribing information but in the local package insert, it states 'food intake both delays and decrease the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity. . The AstraZeneca Hong Kong Limited has clarified that Nexium® tablets can be taken with food or on empty stomach.*
\# *The formulation allows the tablets to disintegrate in non-carbonated water. For details of the method of administration, please refer to the package insert.*
\+ *The capsule can be opened and administered: sprinkle intact granules on one tablespoonful of applesauce and swallow immediately. Do not chew or crush.*

Limitations of PPI[3, 5, 6, 8, 9]

Evaluation for proper compliance and optimal dosing time is the first management step in assessing patients with heartburn not responding to PPI therapy. Yet, of those who have good compliance and been dosed optimally, there are many cases of insufficient symptom control and inadequate clinical response. So, what are the major problems behind? The potential reasons include the inherent pharmacological and pharmacokinetic limitations of PPIs.

1. Lack of a rapid onset of activity - PPIs are acid-labile prodrugs, so currently available PPIs are orally administered as gastro-protected preparations (enteric coated tablets for Pantoloc® and Pariet®; tablets containing enteric coated granules for Nexium® and Takepron OD®). Chewing or crushing the tablets may expose the drug ingredient to the acidic medium of the stomach, accelerating the degradation of the drug and hence the tablets should not be crushed or chewed. Despite the gastro-protective effect, the enteric coatings have the potential disadvantage of delaying PPI absorption.
2. Requirement for acid activation - Once entering into the bloodstream, PPIs can only bind (covalently) with the proton pumps in parietal cells in their activated state, i.e. when they are actively secreting acid. Therefore, it would be better to administer PPIs 30-60 minutes before meal as the proton pumps can be activated by food. The drug will have no use if the proton pumps are not activated. This explains why the effectiveness of the treatment of PPIs depends on the time of administration by the patients.
3. Short dwell time of the drug in the blood - The short half-life property of PPI can lead to inadequate control of the symptoms, especially nocturnal acid breakthrough (NAB) in some patients. This is because PPIs cannot block the newly synthesized proton pumps and those not in their activated state. These proton pumps will continue to secrete acid and lead to treatment failure.
4. Not all proton pumps can be activated by a single meal – with once-daily administration, about 70% of the pumps are inhibited, and with twice-daily administration, 80% are inhibited. It may require several doses to achieve maximum acid suppression and symptom relief, thus limiting their usefulness in on-demand GERD therapy.
5. PPIs are inhibitors of hepatic cytochrome P450 system (CYP450) 2C19 enzyme.[10] Concomitant administration with clopidogrel (a substrate of CYP 2C19) may have a significant reduction of the antiplatelet effect due to a competitive inhibitory effect by the PPIs. It has been confirmed that both omeprazole and esomeprazole may associate with significant drug interaction with clopidogrel, but the interaction is less pronounced with pantoprazole or lansoprazole.

EXAMPLES OF NOVEL DRUG PRODUCTS[11, 12]

Novel drug development in the GI field has been aiming to tackle these limitations, bringing hope to those refractory and uncontrolled GERD cases. Examples of possible therapeutic strategies include:

1. Development of new PPI

As discussed, PPIs have relatively short half-lives after being absorbed from the GI tract. Numerous researches have been conducted to develop PPIs with an extended plasma half-life, so that the duration of action can be long enough to provide an extended acid-suppressing cover throughout the night to the next morning. Tenatoprazole is an imidazopyridine-based PPI and its rate of metabolism is found to be slower than the conventional PPIs, resulting in several folds of extended plasma half-life (8.7 +/- 2.6 hours for repeated administration of 40mg). Another compound under research is called alevium (AGN201904-Z). It is a prodrug form of omeprazole. The compound is stable in acidic medium and is slowly absorbed throughout the small intestine and not just in the duodenum. Once absorbed, it is rapidly hydrolyzed to omeprazole. It exhibits a prolonged half-life (3.8-4.5 hours) compared with conventional omeprazole and therefore provide better nighttime suppression of acid secretion.

2. PPI with a new formulation

Targeting the need to develop a formulation to solve of problem of nocturnal acid breakthrough, dexlansoprazole, which is the more active R-enantiomer of lansoprazole, employs a special

delivery system known as dual-delayed release system.[14] Each capsule can produce two waves of drug release (1-2 hours and then 4-5 hours after dosing). By extending the duration of drug release, one dose of the drug can provide a much longer duration of action, which can target patients with nocturnal GERD symptoms (who may only improve marginally with twice-daily dosing of PPIs) or even some refractory cases. This new drug product has been marketed in the US and Canada, and currently under registration process in HK.

As per mentioned above, the enteric coatings of PPI oral formulation have the potential of delaying PPI absorption and inhibition of the H/K-ATPase in parietal cells requires acid activation. Several new formulations are developed to target the need of rapid onset or meal-dependent issue. Two of the examples include Zegerid® (approved in FDA) and VECAM (under development). Zegerid® is the combination of omeprazole and sodium bicarbonate. Sodium bicarbonate can increase the gastric pH shortly after ingestion. It provides a rapid symptomatic relief before the effect of omeprazole emerges and protects the drug from the degradation by the gastric acid. VECAM is an experimental drug (in phase III trial). It incorporates a 'meal-mimicking agent' (succinic acid) with omeprazole into the drug product. The agent can allow drug administration regardless of meals so as to enhance patient compliance and allow bedtime administration for nocturnal acid breakthrough.

3. A novel class of compounds - potassium-competitive acid blockers (P-CABs)[14]

Drugs of this class block gastric acid pumping by competitively inhibiting the potassium-binding region of the H/K-ATPase on parietal cells in a reversible manner. One of the clear advantages of this new class is that it can offer a very rapid onset of action because it is more stable in acidic environment than PPIs and rapid absorption can be achieved. On-demand therapy will be made more feasible than PPI. These drugs also accumulate within the parietal cell to a much greater extent than do PPIs. Early clinical data showed that nearly maximal acid inhibition effect can be achieved after the first dose of administration. Besides, the duration of activity of P-CABs is directly related to their plasma half-lives which were found to be much prolonged, allowing a more durable acid-suppressive effect, compared to a standard PPI. This may be an alternative to refractory patients or patients with nocturnal reflux symptoms despite standard PPI treatment. A few compounds are currently under clinical trials. The characteristics of the newly developed compounds are listed out in Table 2.

Table 2: Summary of the characteristics of the newly developed compounds

	New PPI	PPI with new formulation	P-CAB
Examples	Tenatoprazole, Ilaprazole, alevium	Dexlansoprazole, Zegerid, VECAM	Pumaprazole (BY841), TAK438, revaprazan (YH1885), soraprazan (BY359)
Market status	Under development	Dexlansoprazole, Zegerid: FDA approved; VECAM: under development	Under development
Faster onset of action	No	No	Yes
Extended plasma half-life	Yes	No	Yes
Extended duration of action	Yes	Yes	Yes
Meal dependency	Yes	No	No

CONCLUSION

Considering its relatively less serious nature, GERD may hardly draw patients' close attention; but neglecting the condition will warrant significant disturbance to normal daily living. PPIs are safe and efficacious for most of the GERD patients. However, there are still a small group of patients with their needs being unmet. The novel drugs may offer new hopes to these suffering patients in the coming future.

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Questions for Pharmacy Central Continuing Education Committee Program

(Please be informed that this article and answer sheet will be available on PCCC website concurrently. Members may go to PCCC website (www.pccchk.com) to fill in their answers there.)

2 CE Units

MC Questions for PJ article

1. ***What will be the optimum duration of Proton-pump inhibitors (PPIs) in patients with gastroesophageal reflux disease (GERD)?***
   A. 1 - 4 weeks
   B. 4 - 8 weeks
   C. 10 – 12 weeks
   D. 16 – 20 weeks

2. ***What is/are suitable option(s) if the patients with GERD do not respond to standard PPI treatment?***
   (1) Switch to another PPI
   (2) Add a H2-blocker
   (3) Increase the frequency to twice-daily

   A. (1) only
   B. (1) and (2)
   C. (2) and (3)
   D. All of the above

3. ***From the point of view of pharmacology, what is the best administration time for a PPI?***
   A. 1 hour after meal
   B. Empty stomach
   C. 1 hour before meal
   D. Take with food

4. ***What is/are the action(s) of PPIs in the process of acid suppression?***
   (1) Inhibit the action of gastrin
   (2) Enhance vagus nerve tone
   (3) Block H/K-ATPase

   A. (1)
   B. (2)
   C. (3)
   D. All of the above

5. ***Which of the following PPIs have a special formulation which allows dispersion in water/fluid for intake?***
   (1) Lansoprazole
   (2) Pantoprazole
   (3) Rabeprazole
   (4) Esomeprazole

   A. (1) and (2)
   B. (2) and (3)
   C. (1) and (3)
   D. (1) and (4)

6. ***Which of the following PPIs need renal dosage adjustment?***
   (1) Lansoprazole
   (2) Pantoprazole
   (3) Rabeprazole
   (4) Esomeprazole

   A. (1), (2) and (3)
   B. (2), (3) and (4)
   C. All of the above
   D. None of the above

7. ***Which one of the following liver enzyme do omeprazole and esomeprazole inhibit?***
   A. CYP450 2C19
   B. CYP450 3A4
   C. CYP450 2D6
   D. CYP450 2A6

8. ***What special formulation does DEXILANT (Dexlansoprazole) employ to enhance the drug delivery?***
   A. Target drug delivery system
   B. Dual-delayed release system
   C. Sustained-release formulation
   D. Prolonged-release formulation

9. ***Which one of the following is NOT a limitation of PPIs?***
   A. Short duration of action
   B. Slow onset of action
   C. Short half-life in blood
   D. Dependent of meal administration

10. ***Which one of the followings are the advantages of potassium-competitive acid blockers (P-CAB)?***
    (1) Rapid onset of action
    (2) Stable in acid environment
    (3) Longer half life

    A. (1) and (2)
    B. (2) and (3)
    C. (1) and (3)
    D. All of the above

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 211(D&T)

Time Matters of Medication: Is It Important?

1. B 2. D 3. A 4. B 5. A 6. B 7. D 8. A 9. B 10. C

Isolation and Purification of Cyclicpeptides from the Root Bark of Lycii Cortex

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ABSTRACT

Lycii Cortex (LyC) is a Chinese medicine used extensively for the treatment of diabetes, lung disease, hematemesis, hypertension and inflammation. Today, more than 50 compounds have been isolated and identified in LyC. Among these compounds, some are octapeptides, which exhibit significant renin and ACE inhibitory activities. Since ACE inhibitors are correlated to the hypoglycemic effect, it is reasonable to speculate that these octapeptides might be responsible for the anti-diabetic function of LyC. In order to obtain sufficient quantity and high quality of the peptides for both *in vitro* and *in vivo* studies of their anti-diabetic effects, it is necessary to extract and purify these substances. However, there is no suitable method available or reported so far. The goals of this study were (1) to extract and isolate the peptides from the bark, (2) to separate and purify them to a level that meets the criteria of the Hong Kong Materia Media Standards, (3) to confirm the structure of purified substances by the LC-MS and NMR. In this proposed study, lyciumins A and B were isolated from the extract solution. After preliminary separation through a Sephadex LH-20, eluent was passed through a C18 column to enrich the content of octapeptides. Purified compounds were obtained through a final purification step on a semi prep-HPLC. Under optimized condition in the LH-20 column, two cyclicpeptides were prepared from the bark of Lycii Cortex in large quantity. After passing through the dispersive solid phase matrix followed by prep-HPLC method, Lyciumins A and its isomer, Lyciumins B, were isolated and obtained from the crude extract. UV-adsorption spectrum of these two fractions showed a characteristic peak of peptide bond; thus, it was assumed the presence of some peptide compounds. After further characterization using the LC-MS methodology, it revealed that these two compounds have the same side chain and ring structure identical to what have been described in literatures for Lyciumins. Through these series of treatment, both Lyciumins A and B were obtained with a purity over 98% was achieved.

Keywords: *Lycii Cortex, cyclicpeptides, Lyciumins Isolation & purification, Sephadex column, LC-MS/MS*

INTRODUCTION

Lycii Cortex (LyC), which is the dried root bark of *Lycium chinesis*, is a well-known traditional Chinese medicine used extensively for the treatment of diabetes, lung disease, hematemesis, hypertension and inflammation for centuries.[1] Modern pharmacological researches have confirmed the outstanding hypoglycemic effect of LyC. Up to recent years more than 50 compounds have been isolated from LyC with their chemical structure well elucidated.[2] Among these reported components, some of them, such as lyciumin A, B, C, D, are octapeptides. These peptides have been found to exhibit significant renin and angiostensin converting enzyme (ACE) inhibitory activities. Since ACE inhibitors are correlated to the hypoglycemic effect, it is reasonable to speculate that these octapeptides might be responsible for the anti-diabetic function of LyC. In order to obtain sufficient quantity and high quality of the peptides for both *in vitro* and *in vivo* studies of their anti-diabetic effects, it is necessary to extract and purify these substances. However, there is no suitable method available or reported so far. The goals of this direct study are: (1) to extract and isolate the peptides from the bark; (2) to separate and purify them to a level that meets the criteria of the Hong Kong Materia Media Standards; (3) to confirm the structure of purified substances by the LC-MS and NMR.

In this study, lyciumins A and B were isolated from the extract solution. After preliminary separation through a Sephadex LH-20 column to remove most interference substances in the extract, concentrated eluent was further passed through a C18 column to enrich the content of octapeptides. Finally, purified compounds were obtained through the final purification on a semi-prep-HPLC. This proposed study included literature search, laboratory work and group discussion. All activities mentioned allowed me to learn the knowledge and techniques for preparation of high quality of bioactive substances from plant extracts. Along this proposed study, dispersive solid phase extraction, freeze dry, step-by-step normal pressure column chromatography and prep-HPLC had been applied and structure of the obtained components was determined.

Overview of Lycii Cortex

Lycii Cortex, name of which in Chinese is 地骨皮, is the root bark of *Lycium chinese* or *Lycium barbarum*, In China, this herb officially recommended for uses in cooling the blood and removing heat from the lung according to the traditional Chinese medicine.[3] A study also proved its positive effects on curing hypertension and diabetes mellitus.[4] Another use of it is acting as an antipyretic to treat pneumonia, night sweating, inflammation and other symptoms.[5]

There are a number of secondary compounds which have been isolated from the Lycii Cortex and they were found to involve chemical components such as alkaloids, amides, coumarins, flavonoids, lignans, organic acids, peptides, sterols, steroids and terpenoids. Lyciumins A, B, C and D are the octapeptides within the Lycii Cortex and they are found to have rennin and ACE (angiotensin I conversion enzyme) inhibitory activities.

Lyciumins and octapeptides from Lycii Cortex

Four octapeptides, Lyciumins A (LyA), Lyciumins B (LyB), Lyciumins C (LyC), Lyciumins D (LyD), were isolated from the root bark of *L. chinense* in the year of 1989 and 1993 and their structures were confirmed by the spectroscopic and computational chemical methods.[6,7] The structures are shown in the figure below: **(Fig. 1)**

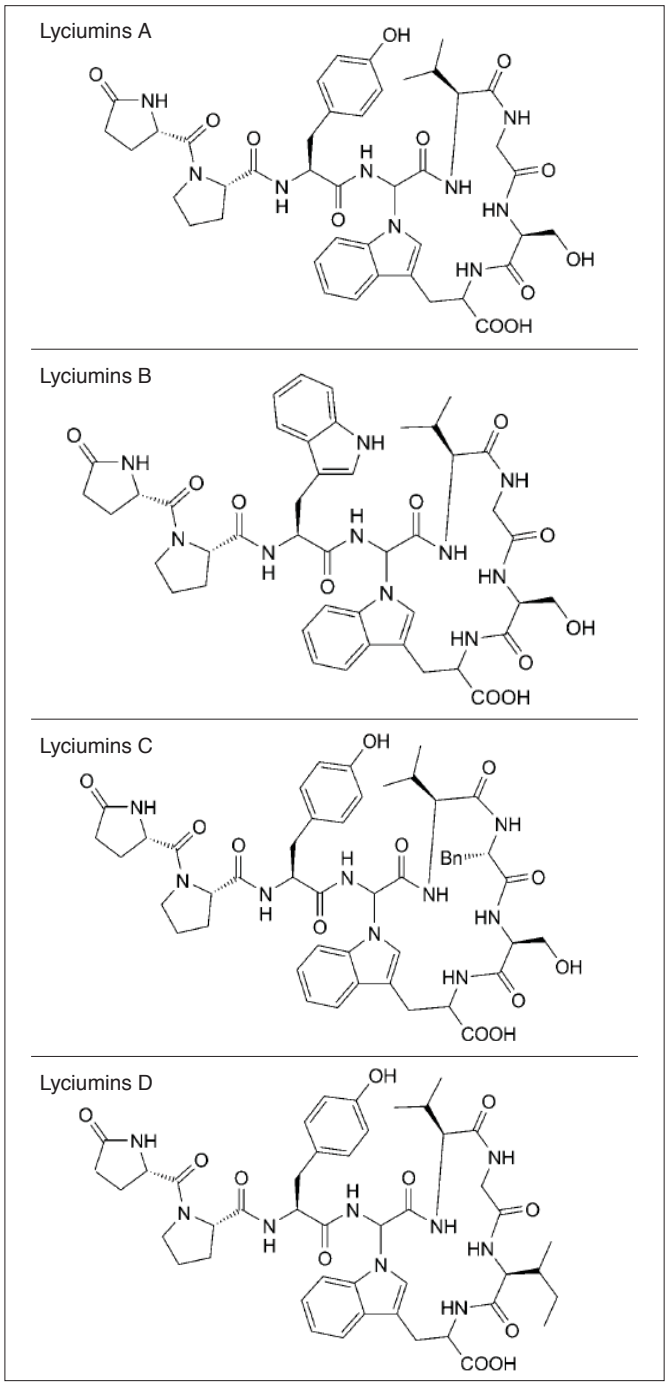

Figure 1: *Chemical structures of Lyciumins*

It is reported that aqueous extract of the leaves of *L. chinense* inhibited the activities of the angiotensin I conversion enzyme (ACE). ACE catalyzes the conversion of angiotensin I to angiotensin II, and the breakdown of bradykinin. Angiotensin II and bradykinin are hypertensive and hypotensive agents, respectively. Lyciumins A and B, could be the hypotensive constituents of genus and have been isolated from Lycii Radicis Cortex as anti-ACE and –Renin substances and their structures have been established.[2] Since ACE inhibitors are correlated to the hypoglycemic effect, it is reasonable to speculate that these octapeptides might be responsible for the anti-diabetic function of LyC. In order to obtain sufficient quantity and high quality of the peptides for both *in vitro* and *in vivo* studies of their anti-diabetic effects, it is necessary to extract and purify these substances.

Chromatography methods used for herbal drug identification and characterization

Sephadex LH-20 Column Chromatography

Sephadex LH-20 column chromatography offers several features which make it particularly useful in steroid assay procedures such as competitive protein binding and radioimmunoassay. Sephadex LH-20 is useful for both analytical and industrial scales for the preparation of molecular sizing of natural products such as steroids, terpenoids, lipids, and low molecular weight peptides closely related molecular species. Due to the unique physico-chemical properties of this medium, it can be used either during initial purification prior to polishing by high performance ion exchange or reversed phase chromatography, or as the final polishing step.

High-performance liquid chromatography (HPLC)

HPLC is one of the most wildly used chromatographic techniques for herb analysis. It can help to identify, quantify and purify the herb extraction with good suitability and high precision. In general, with variation of columns and detectors, HPLC can be used for almost all the constituents with purposes of separation and quantification for herb extractions. HPLC is easy to operate and the sensitivity is relatively high. It is applicable for a large range of substances including both charged and neutral molecules. Large variation of the mobile phase provides good conditions for exploring the best separation methods. For the target compound in this experiment, the extraction of the herbs is polar and reversed-phase chromatography may be the most suitable method. With fixed column, the number of theoretical plates would be fixed. Thus, a better separation condition can be experimented by altering the composition of mobile phases, flow rate, temperature or pH of the mobile phase. In order to find the optimal condition for separation, different combination could be used to see the separation effect. Different techniques can be applied such as isocratic elution and gradient elution to increase the efficiency. However, the consumption of large amount of solvent would be the disadvantage of this method.

Liquid chromatography-tandem mass spectrometry (LC-MS-MS)

Previous studies of our group had developed the LC-MS-MS method with high specific multiple-reaction monitoring.[6,7] This method was sensitive, reproducible and accurate. The detection limit is lower than the HPLC method. However, as a pair of isomer, the Lyciumins have the same pairs of m/z

in 874 and could not be differentiated by MRM, thus a longer separation time was needed in this method. The high expenses cost by this method would be another disadvantage.

Objectives of this Study

There is a need in developing the optimal method in order to have a qualitative and quantitative analysis of the octapeptides because lyciumins were showed to be the some significant constituents under the constituent profiles of Lycii Cortex, and the renin activities and inhibitors of ACE suggested that the lyciumins is related to the anti-diabetic function of LyC. However, since currently there is not any suitable method reported for the analysis, the objectives of my direct study would be to extract and isolate the octapeptides from the root bark of *Lycium Chinese* or *Lycium barbarum*, and afterwards purify them to meet the criteria of the Hong Kong Materia Medica Standards and finally, confirm the structure of the purified substances are the octapeptides by using the LC-MS.

METHODOLOGY

Experimental procedures

Preparation of Supernatant Solution

First, approximately 16 g of crude extract powder were dissolved into 400 mL of pure water and the solution was poured into eight 50 mL-test tubes for centrifugation in order to obtain the supernatant (S_o). The solid which could not dissolve into the water was removed from the solution. After that, 10 g of polyamide, which acted as an adsorbent, was added into the solution and mixed for two hours under 25ºC using the magnetic stirring apparatus. The mixture was then filtered and the adsorbent was put into pure water for around 5 minutes. The washed adsorbent was then reserved. Pure water was added to the S_o together with 6 g of polyamide. The mixture was stirred for another two hours and then filtered after stirring. The absorbent was reserved under the same procedure as previously mentioned. The supernatant obtained was used for the preparation of Cyclicpeptides.

Preparation of the Cyclicpeptides

Sample extraction

To extract the cyclicpeptides from the samples, first the S_o solution from the previous steps was freeze-dried for 4 to 5 days to turn into powder, and then the powder was dissolved in 50 mL of 30% methanol. The solution was centrifuged at ca. 4000 rpm for 15 minutes. The white precipitation after centrifugation was separated. Then, another 50 mL of 30% methanol was added into the remaining white precipitation in order to collect the supernatant.

Sephedex LH-20 separation procedures

Then, Sephedex LH-20 was used for the separation. Each time, about 6 mL of the collected supernatant was loaded to a column packing with Sephedex LH-20. Then, 30% methanol was added to act as the mobile phase of the chromatography. The first 50 mL collected was discarded because it was the dead volume of the column. After that, another 60 mL collected was discarded as well because there was no target compounds contained in that portion, and the fraction that was useful appeared after that. Thus, the fractions with 10 mL per tube were collected from the 110 mL to the 230 mL, and the fractions with the same order were combined together when repeating the above procedures. After that, the solution from the useful fraction obtained was analyzed using HPLC, which aimed to test the occurrence of Lyciumins A (LA) and Lyciumins B (LB). Then according to the abundance of LA and LB in the solution, the fractions were classified into two groups and they were then loaded onto two respective small cartridges. After that, they were rinsed with 50 mL 30% methanol first, and then the two cartridges were eluted respectively with 50 mL of 50% and 50 mL of 80% methanol. In order to remove the methanol, rotator was used to dry the elution under room temperature. Finally, the eluted products were freeze-dried to get the crude powder for further separation in the semi prep-HPLC.

High Performance Liquid Chromatography procedures

Mobile phase preparation

First, the mobile phases for separations of LA and LB were prepared. For LA, the mobile phase was made of 25% ACN and 75% of 0.2% formic acid aqueous solution; whereas for LB, the mobile phase was made of 27% CAN with 73% of 0.2% formic acid aqueous solution. The solutions for mobile phase, after adding the components accordingly, were under sonication for 30 minutes before going to the pump.

Separation procedures

Then, for the separation, Waters 486 and Waters 515 HPLC Pump were used. The signal wavelength for peptides was measured to be 270. The target peaks shall be tested using the Angilent 1100 to confirm the peak areas before using the prep-HPLC.

The flow rate was set at 3.5 mL per minute and 200 µL of the sample was injected once at most. Then, the signals of the elution were collected and then tested by the LC-MS and analytical HPLC, in order to confirm the purity and the structure of the compounds involved. Finally, the final product white powder was obtained using freeze-drying.

RESULTS AND DISCUSSION

Determination of Lyciumins by Sephedex LH-20 separation

Preparation of sephadex LH-20

The stationary phase or adsorbent in column chromatography is a kind of solid material. The commonly used stationary phase for column chromatography is sephadex, which is a fine powder or gel comprising of microporous to increase its surface area. The principle of mechanism of separation of compounds with this stationary phase is based on the size differences of molecules as well as their molecular shape, functional groups, chain lengths, degree of unsaturation or the partition efficiency between the molecules and the eluent. **Fig. 2** below shows how mixed molecules are separated from each other in a column. Because of different partition coefficient forces, molecules of particular interest could be separated from the others and eluted in different fraction of eluents.

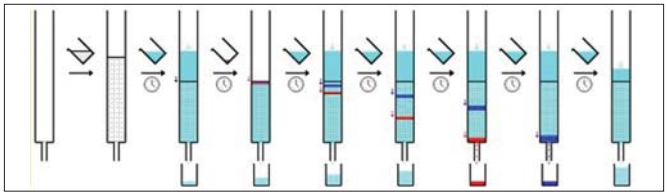

Figure 2: *Separation of mixed molecules based on their physicochemical nature and their partition coefficient forces to stationary phase in the column*

In this study, the Lyciumins have the similar molecular weight but different polarity. Hence, a reversed-phase solvent was used to elute the weak polar compounds to come out first followed by other polar compounds from the column. To achieve this purpose, mixture of methanol/water solution was used. It was composed of 30% methanol in water throughout the elution process. Added volume of the dissolved sample was in the range of 1-2% of the total bed volume, which was about 5-7 mL of supernatant in our case per time. In order to maximize the life-span of column, the dissolved sample was centrifuged and filtered to remove undissolved material before adding into the column. Besides, the maximum flow rate was properly under controlled because a finite time was required for the analytes to equilibrate between stationary phase and mobile phase. In general, the lower the flow rate, the better the resolution. To convert flow rate for column of different dimensions, the following linear flow rate equation was used:

Volumetric flow rate (cm^3/h) / Column cross-sectional area (cm^2)

Thus, flow rates of 1-10cm/h were used to ensure the different compounds were well separated. The fractions with 10 mL per tube were collected so as to separate different target compounds into different tubes. The reason of it was because we didn't know when Lyciumins would be eluted first so we should separate the elution into different test tubes for the further testing. Since Sephadex LH-20 could be regenerated by washing the column 2-3 times with the bland eluent such as NaOH-NaCl/Water solution. A solution comprising of 8 g of NaOH, 30 g of NaCl in 1000 mL of pure water was used.

During elution, bubbles might be formed or trapped in the Sephadex LH-20 column. If this occurred and if the bubbles were formed on the top of the column, slight stirring with a glass rod could overcome this problem. If the bubbles were trapped at the bottom of the column, sufficient mobile phase should be added until the bubbles were eluted. If the bubbles were trapped in the middle of the column, the column should be re-packed again.

Determination of Lyciumins by Analytical-HPLC

HPLC-data

The analytical-HPLC is used for quantification and identification of compounds. Different fractions of the solution were tested in the fixed conditions such as type of column, solvent system, gradient, flow rate and detection. The conditions are shown in the following Table:

Solvent A	0.2% formic acid
Solvent B	Acetonitrile
Ratio of Solvents	A:B=3:1
Flow rate	3.5mL/min
Inject volume	10 µL
DAD Signals	270 nm

Description of the HPLC-chromatogram

Since there is a characteristic UV-end absorption of peptide compounds, the Lyciumins can be predicted by using UV-absorption of the constituent amino acids to see whether exhibit a UV absorption peak near 280 nm occurred.

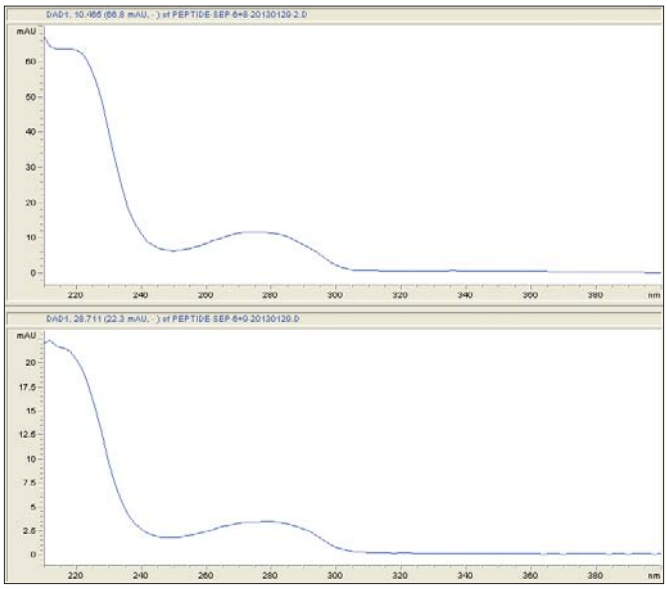

Figure 3. *UV-absorption of Lyciumins A (Top) at 10.465 minutes and Lyciumins B (bottom) at 28.711 minutes*

The above figure shows that the selected peak from the results has the constituent amino acids UV-absorption so we targeted it should be octapeptides. In order to find out Lyciumins A and B consist in which fraction of the test tube, two charts have been plotted based on the Peak Areas against Volume.

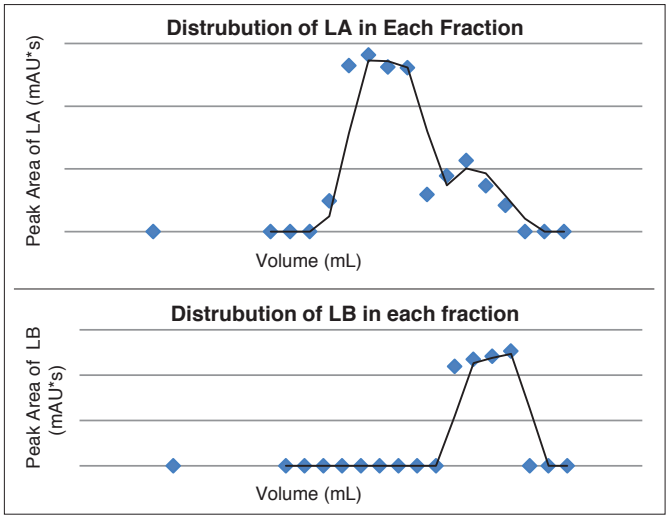

Figure 4: *Appearance of Lyciumins in each fraction of the eluents. Top: Lyciumins A; Bottom: Lyciumins B.*

Based on the UV-adsorption of certain peak **(Fig. 3)**, we can find out the peak area of each fraction. Since Lyciumins A appears in the fractions from 140 to 230 mL and Lyciumins B appears in the fractions from 200 to 230 mL, both Lyciumins A and Lyciumins B are overlapped from 200 to 230 mL **(Fig. 4)**. In this case, the fractions from 200 to 230 mL were combined together and the fractions from 140 to 190 mL were combined as another group.

Determination of Lyciumins by PREP-HPLC

HPLC-data

Preparative HPLC is used for the isolation and purification of compounds in pharmaceutical industry. Since there are three important parameters to judge the result of a preparative run which are purity of the product, yield and throughput, this

prep-HPLC method is very significant to the final result. The conditions of prep-HPLC are similar to that mentioned before. However, Waters 486 and Waters 515 HPLC Pump were used so the mobile phase should be prepared manually.

Description of the HPLC-Chromatogram

The two groups of elution were then loaded on two small cartridges before using the prep-HPLC. After washing with 50 mL 30% methanol, both cartridges were eluted with 50 mL 50% and 50 mL 80% methanol, respectively. After that, the Lyciumins will be confirmed by HPLC to see whether the Lyciumins appear in which methanol/water ratio. The result shows that the majority of Lyciumins A and B can be found in 50% methanol only. The Lyciumins A and B were then collected in different test tubes in accordance with the peaks shown below in **Fig. 5**. The finally step was to obtain dry power through freeze drying the elute and re-dissolving in pure water for analytical purposes whenever necessary.

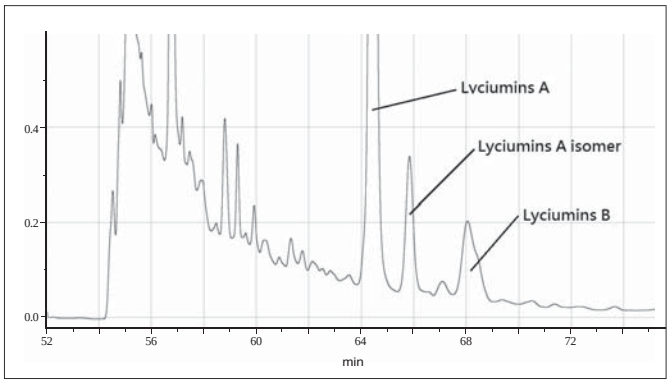

Figure 5: *A HPLC chromatogram of aqueous extract of Lycii Cortex.*

Determination of Lyciumins by LC-MS

Identification of Lyciumins A and its isomer

The important fragments of Lyciumins A and its isomer are 874, 503, 486, and 468 m/z. **(Fig. 6)**

In the MS, the Lyciumins A was broken down into two parts: the ring part and the side chain part (372 m/z). Normally, the ring part would lost a fragment of 17 (NH_3), and then lost another fragment of 18 (H_2O). **(Fig. 7)** Therefore, 503, 486, 468 signals were observed in the MS spectrograms.

Identification of Lyciumins B

To compare with literatures, the only difference between Lyciumins A and B is the side chain part which has a signal at 395 m/z **(Fig. 6)**.

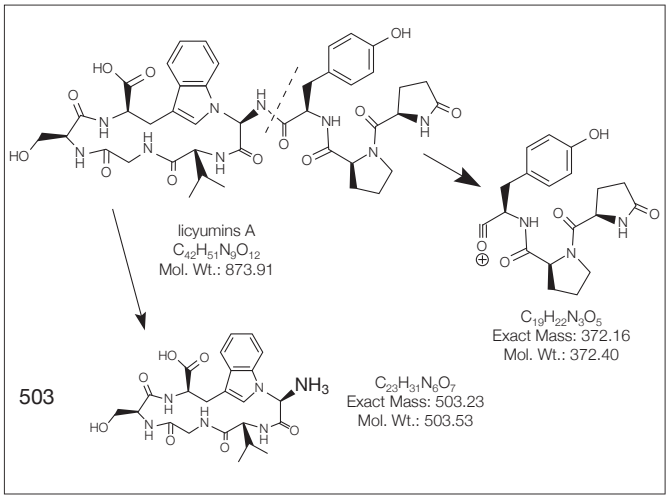

Figure 7: *The breakdown of lyciumins A.*

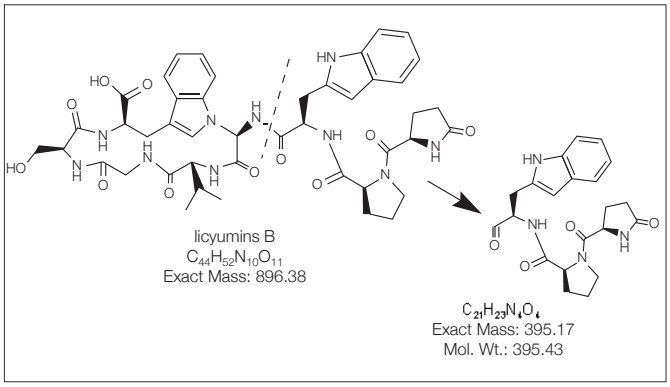

Figure 8: *The breakdown of lyciumins B.*

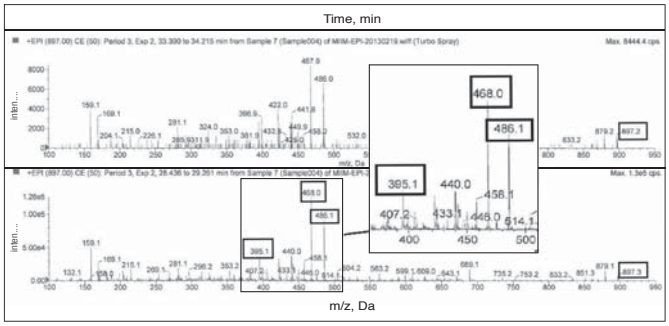

Figure 9. *LC-MS/MS analysis of Lyciumins A.*

In the MS, the ring part of the Lyciumins B is the same as in Lyciumins A but their side chain part (395 m/z) was different. **Fig. 8**. Hence, occurrence of peaks due to the breakdown a substance could be used for differentiating Lyciumins B from Lyciumins A by means f LC-MS2 analysis **(Fig. 9)**.

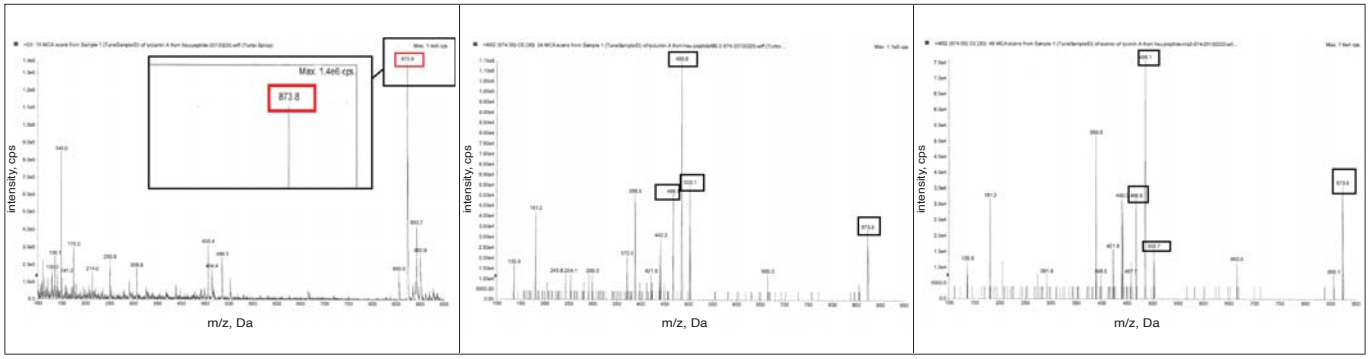

Figure 6: *LC-MS spectrogram of Lyciumins A (Top), and LC-MS2 spectrogram at 874 m/z of different isomers of Lyciumins. Lyciumins A (Middle); Lyciumins B (bottom)*

Purity of the Lyciumins

Purity of the freeze dried materials were analysed with uv spectrometry. Results of maximal absorption are shown in shown **Fig. 10**.

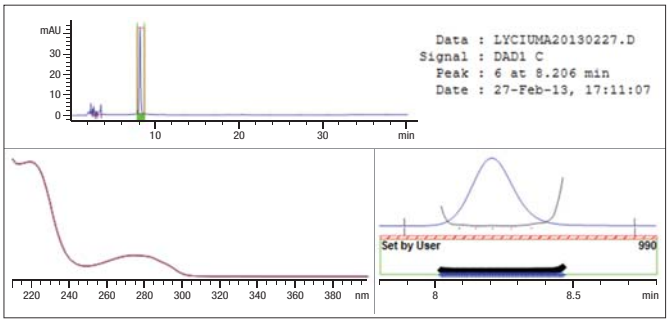

Figure 10. *UV absorption spectrum of the freeze dried materials prepared from fraction 9 of the elute*

The result of Lyciumins A shows that all 67 spectra were within the threshold limit so the purity factor was within the threshold limit. The Lyciumins A isomer and Lyciumins B showed the similar results that all spectra were also within the threshold limit, respectively

The determinations of the purity of the peak are the position of threshold curve and similarity curve and the difference of purity factor and threshold. For these three purity results, the threshold curve and similarity curve are very smooth without cross-link and the threshold curves are on top of the similarity curves. Also, the purity factors are larger than the threshold. Thus, it can be concluded that the Lyciumins A, B are pure enough

Other findings in this study

In this study, both Lyciumins A and Lyciumins B were identified and purified. One of the discoveries in this study is that there were two unknown compounds presented in 80% methanol/ water. These two unknown compounds had the same UV-adsorption of peptides. The unknown compound was eluted at 27.332 minutes while an other unknown compound was eluted at 30.963 minutes **(Fig. 11)**.

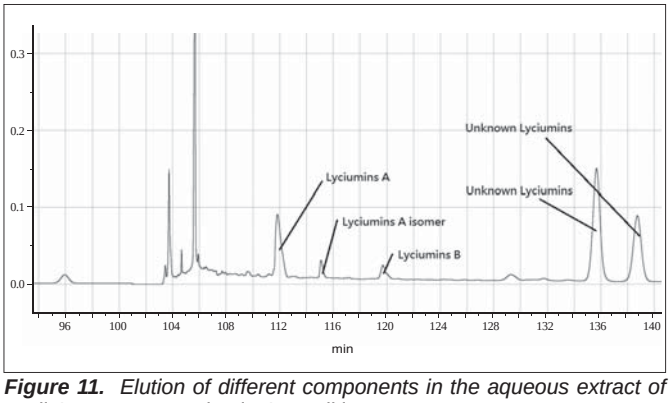

Figure 11. *Elution of different components in the aqueous extract of Lycii Cortex at an optimal LC condition.*

Also, the unknown peptides can be collected from the prep-HPLC. A further study in these two compounds would provide further information for determination of their structure

CONCLUSION

In a recent literature review by Choudhary and Sekhon, they have pointed out that herbal medicine has become a popular therapeutics in many countries. However, its complexity also imposes some difficulty in their quality control.[8] According to the results obtained from a series of experimental works under optimized condition in a Sephedex LH-20 column, two cyclicpeptides have been prepared from the bark of Lycii Cortex. Both Lyciumins A and its isomer, Lyciumins B, were isolated and obtained from the crude extract after passing through the dispersive solid phase matrix followed by prep-HPLC method. UV-adsorption spectrum of these two fractions showed a characteristic peak of peptide bond; thus, it was assumed the presence of some peptide compounds. After further studies using the LC-MS methodology, it was revealed that these compounds have the same side chain and ring structure identical to what have been described in literatures for Lyciumins. Therefore, we were quite sure the isolated compounds are Lyciumins A and B. Finally, the purities of both Lyciumins A and B were determined by HPLC and they all exceeded 98% of purity.

Author's background

*Both **Mr HSU Wing Leung** and **Miss DI Rui** hold a BSc degree in Chemistry. They were undergraduate students in the Department of Biology and Chemistry, City University of Hong Kong before 2013. This is a piece of their direct study conducted under Dr HY Cheung's supervision. Mr HSU is now doing a Pharmacy Degree in Sunderland University, UK while Miss DI is working as a Research Assistance in Dr Cheung's laboratory. **Ms LI Yuanyuan** is currently a PhD candidate. She works on a project relevant to the quality control as well as the isolation and purification of bioactive components from the Lycii Cortex. **Dr. CHEUNG Hon-Yeung**, who is an Associate Professor of Pharmaceutical Microbiology & Biotechnology at the City University of Hong Kong since 1989, is a manufacturing pharmacist and biotechnologist. He has more than 40 years of work experiences in industries, academic and consultancy jobs. He was an expert witness in court and a member of the Biotechnology Committee for Hong Kong and Shenzhen Government. Dr. Cheung has published more than 2200 papers and articles in many prestigious international journals. His email address: bhhonyun@cityu.edu.cn.hk*

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Recent Studies of Anti-Aging Herbs: The Biomedical Functions of Gingko, Lycium Barbarum Fruitus and Ginseng

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ABSTRACT

Aging is a global problem in today's world. Although it is a natural process, it could be speed up by many factors, including telomere length and telomerase activity, oxidative stress and decline of immunity making the mechanism of aging much more complicated than its normal process. Since the life expectancy of modern people has increased longer in the last fifty years, there are a big proportion of aging populations facing some sort of health problems, which give rise to a social problem simultaneously. Therefore, there is a big demand on promoting "healthy aging" and retarding the aging rate. In ancient China, there was literature indicating the use of medicinal herbs which are good to promote anti-aging function and offer a healthy aging. Several representative examples have been chosen and their functions are reviewed. Through summarizing their functions and mechanism of these herbs, it is concluded that these traditional Chinese medicines provide protection on (1) lowering the formation of free radicals and glycosylation products, (2) regulating the metabolism, (3) improving the immunity, (4) protecting the neuronal system. Because of these effects, these herbal substances could regulate life activities and could be taken as our daily supplementary food.

Keywords: *Anti-aging herbs, telomerase activity, oxidative stress, healthy life, supplementary food, Ginkgo, Lycium barbarum, Ginseng, glycosylation*

INTRODUCTION

Aging is a natural and irreversible process that shows progressive degeneration and malfunction in life. As there is an occurrence of error or damage which is beyond repairable in gene level, it implies down grading of physiological functions and eventually affects the quality of one's life; the probability of death thus increases. The deleterious syndromes can be present in different aspect in individual, such as occurrence of neuro-degeneration,[1] immunity and cardiovascular diseases.[2]

There are reports suggesting aging can be caused by different factors including inheritance which genes may cause pre-maturation aging, gene mutation and telomerase activity. Also, DNA sequence may be damaged by free radical and reactive oxygen species (ROS).[3] Therefore, any factor that may relate to gene regulation and expression, protein function, and eventually cause cell death may give rise to aging. As a natural force, aging helps to maintain the continuity of species, as older individuals develop poor reproducing ability and are easier to be attacked by disease. However, in some country, aging become a social problem, for it declines the productivity when more citizens is being elder.[4] Therefore, it is important to expand the lifespan of human beings in terms of maintenance of health by the use of herbs.

MECHANISMS OF AGING

Telomere, telomerase and aging

At the end of chromosome, there is telomere. Telomere is a protein non-coding DNA region, providing protection to chromosome from degradation of nuclease. In general, telomere will be shortened in every round of replication. The shortening of telomere may cause loss of function if the deletion is overlapped with functional gene.[5] In order to fill in the shortened region, telomerase is needed to take the action. Shortening of telomere may lead to instability of chromosome and alternation of gene expression. It will also cause cell apoptosis and senescence.[6,7] Reports suggest telomere length may highly relate to implication of disease and lifespan by studying the telomere length and cell survival rate.[8]

However, from some reports, research groups suggest telomere length has no relationship with the lifespan and even indirectly proportional to longevity in some cells such as B-lymphocyte.[9] In addition, telomerase is usually expressed in germ cells instead of somatic cells due to the rapid occurrence of cell division in gonads. High expression of telomerase in somatic cells will leads to the development of cancer.[10]

Oxidative damage and aging

Biochemical pathway is a reaction related to electron transportation. In general, substrate acts as an electron donor while product acts as an electron acceptor. Therefore, compound in the organisms can be interfered by foreign electrophilic chemicals, such as free radical also called reactive oxygen species (ROS).[11] ROS is mainly absorbed by the body in form of oxygen in atmosphere. Besides from nature,

ROS can also be produced in body, such as formation of peroxides from lymphocytes or during oxidative respiration.[12] ROS can attack nucleic acids, side chains of amino acids and unsaturated fatty acid. By this way, mutation may occur as sequence of DNA is altered. Besides damaged proteins and lipids may interfere other biochemical pathways.[13]

ROS can also exert impact on the membrane system of the cell and organelles, especially mitochondria. In additional, change of maintenance of cell membrane may cause apoptosis. As a consequence, accumulation of cell death will lead to aging.

Mitochondria dysfunction and aging

Mitochondria are organelles for respiration in eukaryotes, which consumes sugar and oxygen to produce energy. There are large amount of mitochondria in tissue which is metabolically active, such as neurons, muscle and liver cells. If it is involved in the process of the electron transport chain and combing the oxygen and hydrogen ions to form water, it will generate lots of ROS during the process.[14]

There are four protein complexes: I, II, III, IV, which are embedded in the cristae membrane of mitochondria. Most of them can generate ROS during electron transport chains, peroxide can be reduced by superoxide dismutase (SOD).[15] However, activity of SOD will be reduced along aging. Accumulation of ROS can attack the lipid layers of mitochondria membrane and thus lead to malfunction of mitochondria.[16]

In addition, aging is related to efficiency of energy production. Damaged mitochondria are digested by the concentration of lysozyme and activity declines with aging.[17] Therefore, dysfunctional mitochondria will be accumulated and produce more ROS instead of energy during aging. Some reports also claimed damaged mitochondrial DNA will stimulate the release of calcium ions from the vacuole which will trigger the release of cytochrome C from the mitochondria, resulting in apoptosis.[18] It can also be Ca^{2+} independent. As Bax and other pro-apoptotic protein members will be up-regulated, under the cell is seriously damaged, it will form pores on the mitochondrial membrane,[19] thus trigger the release of cytochrome C and apoptosis.

Glycosylation and aging

Biochemical reaction in living things is implanted by protein. As a product of chain of amino acid, it contains lots of amino group and carbonyl group which are protonated or ionized respectively. In general, carbohydrates can be attached to the amino acid side chain, but sometimes, reducing sugar can attach to the amino acid non-enzymatically. Once the carbonyl of glucose formed a bond with the amino group, an Amadori product (a ketoamine) is formed. Hydrogen in Amadori products can rearranged so that an advanced glycosylation end product (AGEs) is formed and it is irreversible.[20] Besides protein, lipids are also the targets to being glycosylated.

When the AGEs are formed, cross link between proteins and lipids will lead to loosely connection between connective tissue. Therefore, the skin and muscle become inelastic.[21] It has also been found that AGEs level is higher than normal in diabetes patients.[22] It is also believed that AGEs will enhance the opportunity of having neurodegeneration disease, such as Alzheimer's disease.[23] As AGEs can generate beta-amyloid peptides, which is able to stimulate the inflammatory effect through NF-kB pathway and forms a plaque in cerebral cortex and hippocampus.[24] Thus, AGEs can lead to degeneration of organs and systems, such as cardiovascular system, urinary system and nervous system.

Hormone and aging

Hormone is a messenger regulating the systems function normally by cooperating with its corresponding receptor. Hormone level and receptor amount may alter with aging. For example, there is down-regulation of vasopressin V2 receptor in elder kidney,[25] therefore the kidney cells cannot sense the arginine vasopressin (AVP, also known as anti-diuretic hormone ADH), and thus lead to hyponatremia.[26] Melatonin (MEL) is another example that will decline with aging, and lead to age-related disease. MEL can act as anti-oxidant to be a free radical scavenger, and thus maintain the activity of SOD, catalase (CAT) or other anti-oxidant enzyme to protect the chromosomal DNA or mitochondrion from free radical.[27] On the other hand, there are studies suggesting that increase of glucocorticoid level will lead to age-related disease, such as Alzheimer's disease by alteration of anti-oxidant enzyme capacity.[28] Thus hormone level fluctuation with aging may also be a factor that accelerates aging.

Immunity decline and aging

Immunity is an important system that defenses the body from foreign pathogens. It can be divided in innate immune and adaptive immune. In human or other mammals, the adaptive immune is the majority and can be subdivided into humoral immunity and cellular immunity which are responsible by B-lymphocytes (B-cell) and T-lymphocytes (T-cell) respectively.

There are studies reporting T-cell proliferation will decline with aging,[29] which may be caused by the change of CD4: CD8 ratio (both CD4 and CD8 are receptor on helper T-cell and cytotoxic T-cell respectively), cytokines are released by helper T-cell to promote clonal expansion of other lymphocytes. However, in elderly, CD4 is decreased in helper T-cell.[30] Moreover, interleukin-2 (IL-2) and the amount of its receptor is declined in elderly, thus decrease of cell proliferation and more susceptible to antigen.[31]

ANTI-AGING HERBS

There are many kinds of anti-aging medicinal herbs. Here are some examples that are popular, effective and easy-to-find in the market.

Ginkgo

Ginkgo biloba is also called maidenhair tree, the only plant belonging to order Ginkgoales (Fig. 1). It is native to China and distributed around Japan and Korea. Since the ancient time, ginkgo has been used as traditional medicine in China. Nowadays, ginkgo trees have been planted overseas, such as Europe, North America, New Zealand.[32]

Figure 1: *Photos of Ginkgo and its dried leaves.*

Ginkgo extract contains terpene lactones which include ginkgolids A, B, C, J, M and bilobalide, and flavonoid glycosides.[33] Both terpene lactones and flavonoids are functional factors to extend life span. Terpene lactones can act as platelet activating factor (PAF) to reduce platelet activation and thus arouse blood aggregation in blood vessels, reducing stroke in circulatory system and improve blood circulation. Bilobalide can reduce cerebral edema produced by triethyltin, decreases cortical infarct volume in certain stroke models and reduce damage from cerebral ischemia.[34] Flavonoid glycosides can carry out antioxidant effect by enhancing the expression of antioxidant protein, such as superoxide dismutase and glutathione, it can also interact with ROS directly in order to reduce damage of cells.

Several protective functions of ginkgo have been reported:

1) Cleaning of free radical, hence reduce ROS level and chance of cell membrane lipids peroxidation.[35]
2) It can prevent diabetes by reducing AGEs level which can lower the chance of diabetes nephropathy formation.[36]
3) Act as prostacyclin, a vasodilator, anti-PAF activity, improve blood circulation.[37]
4) Increasing mitochondrial respiration by protecting the oxidative phosphorylation pathway, thus maintain sufficient ATP level.[38,39]
5) Enhance neuronal plasticity.[40,41]
6) Anti-inflammatory and protective actions against brain by inhibiting PAF damage through ginkgolides.[42]
7) Increasing ATP level, retard neuronal apotosis.[43]
8) Inhibition of beta-amyloids (Aβ) aggregation in neuroblastoma cells.[44]

From the biochemical point of view, ginkgolides and flavonoids can be scavengers of superoxide and hydroxyl radicals.[44] Therefore, it is reducing ROS level in the body. By this way, it is protecting mitochondria and maintaining sufficient ATP production which is good for cell maintenance and inhibit apoptosis.[45] Numerous experiment have used model organisms to show that ginkgo extracts can retard the rate of neuronal degeneration by inhibiting the production of neurotoxins.[46,47] In addition, it inhibits the beta-amyloid aggregation and caspase activation, both of which lead to neuronal cell death.[48] Therefore, it can lower the chance for having neurodegenerative disease, such as Alzheimer's disease.[49]

In addition, ginkgo extract can suppress the release of adrenocorticotropic hormone, corticosterone, norepinephrine by controlling the production of corticotropic releasing hormone.[50]

In short, ginkgo extract can maintain the function of circulatory system, nervous system and also provide antianxiety effects. Hence, increase longevity of the user.

Lycium Barbarum Fruitus

Lycium Barbarum Fruitus, also called Gou Qi Gi in Chinese, not only serves as a common Chinese cuisine but also a traditional Chinese medicine (Fig. 2). It is believed that the fruit of this herb can nourish the eyes and liver by balancing Yin and Yang from the point of view of Chinese medical doctor and philosophy. It contains lots of valuable contents, such as vitamins, carotene, zeaxanthin, flavonoids[51] as well as different kind of polysaccharides. These polysaccharides that produce in lycium are also called Lycium barbarum polysaccharide (LBP), include D-rhamnose, D-xylose, D-arabinose, D-frutose, D-glucose and D-galactose.[52]

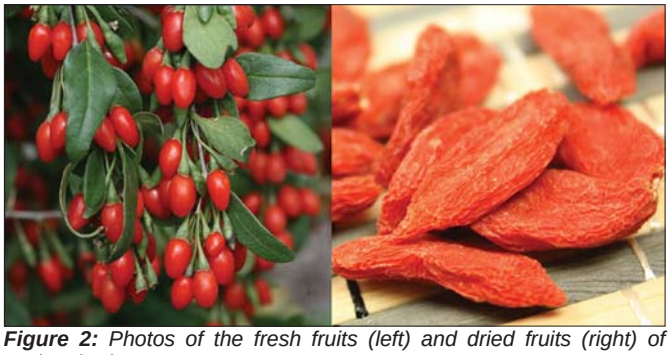

Figure 2: *Photos of the fresh fruits (left) and dried fruits (right) of Lycium barbarum.*

Numerous reports claimed that LBP can provide anti-aging function by its antioxidant effect.[53,54] There are many LBP fractions: such as LBP_{3p} and LbGp1-5.[55] They are the carbohydrates with different type of linkage with different carbohydrate compositions. It is claimed that crude extract of LBP is more effective than purified LBP in function of hypoglycemic and hypolipidemic effect.[56]

LBP contains antioxidant activity and stimulatory ability which can help to maintain health. Its function can be divided as "Indirect enhance immunity" and "direct cellular effects".[57]

For "indirect" effect, it can stimulate the immune cell such as splenocytes and B-lymphocytes proliferation in vitro by up regulating of activator protein-1 (AP-1) and nuclear factor-kappa B (NF-kB).[58] It can also stimulate the release of interleukin-2 (IL-2) and tumor necrosis factor alpha (TNF-a), that may lead to apoptosis of damaged cells which can prevent the formation of cancer.[59]

For "direct" effect, it can stimulate the production of enzyme that is anti-oxidizing, such as SOD, catalase and glutathione peroxidase.[60] On the other hand, it can trigger the release of B cell lymphoma 2 (bcl2) which is anti-apoptotic. In addition, LBP may also be an anti-oxidant to remove the ROS,[61] it can protect DNA from oxidative damage by peroxide which is suggested by studying the effect of superoxide on mouse

testicular cells.[62] Moreover, present of LBP can effectively decrease the blood glucose level as well as lipid. Diabetes is a common disease in modern society, which is caused by hyperglycemic and hyperlipidemic.[63] Studies report that LBP can reduce the blood glucose level which lowers the chance of getting high AGEs level and peroxidation of lipid, preventing the users from several disease, such as coronary disease or diabetes.[64, 65]

Recently, *Lycium barbarum* had been studied on the function of neuronal protection.[66] As mentioned at the previous chapter, one of the factors that leads to neurodegenerative disease is presence of Aβ, which will activate pro-apoptotic pathway. Studies conducted on LBP function suggest it can inhibit homocysteine and Aβlevel, preventing the stimulation of caspase and apoptotic pathway.[67]

In short, fruit and extract from *Lycium barbarum* contains abundant of LBP which acts as an anti-oxidant, for removing the ROS in the body. In addition, it is a good hyperglycemic and hyperlipidemic agent which can maintain health in the circulatory system and other organs. Last but not least, it can trigger immune cells proliferation, anti-tumor and restore neuronal function through regulating pro-apoptotic genes, reducing the chance of getting disease and increasing life span.

Ginseng

Ginseng, belonging to family *araliaceae*, genus *panax*, has been used as a traditional medicinal herb since ancient time in China (Fig 3). It is widely distributed over the world, the most popular is Korea, China and the US, and their chemical constituents are different from each other which depend on the soil composition.[68] The most bioactive chemical ingredient in ginseng is named ginsenosides, and can be categorized in three main groups: protopanaxadiols (PPD), protopanaxatriols (PPT), and oleanolic acid derivative. Both PPD and PPT are ginsenoside compound that has a steroid structure.[69,70] The detailed chemical constituents in each category are listed in **Table 1**. Depending on the content of their composition, ginseng from different region may give function with a bit differences.

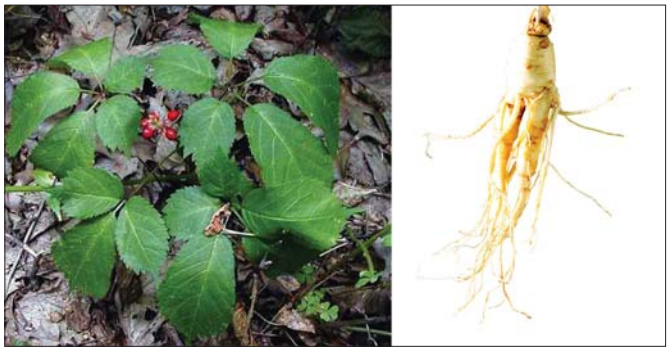

Figure 3: *Photos of a Ginseng plant (left) and its root (right)*

Table 1. Chemical constituents of each category of ginsenosides based on their chemical structure

Constituents	Examples
Protopanaxadiols (PPD)	Rb1, Rb2, Rc, Rd, Rg3, Rh2
Protopanaxatriols (PPT)	Re, Rf, Rg1, Rg2, Rh1
Oleanolic acid derivatives	Ro

Ginseng can carry out many protective functions. In Ming dynasty (1368-1644 in China), Li Shizhen, a famous Chinese medical doctor reported ginseng can be used to treat diabetes in Ben Cao Gang Mu. By modern technology, it is reported it can be a hyperglycemic agent. That rats had been fed with 3-9 g of American ginseng had shown reduced blood glucose level after glucose challenge.[71] It is believed that ginsenosides such as Rh2, can stimulate the ATP production which provide more energy to the cell as well as inhibit the mitochondrion uncoupling protein 2 (UCP-2) which is reported as one of the major factor causing diabetes.[72] In addition, ginsenosides can increase expression of glucose transporter, GLUT4 in tissues especially in muscle and fat,[73] therefore remove glucose from blood and restore to normal level.

Also, ginseng is a good antioxidant, which is supported by many studies. Research suggest ginsenosides can lower the hydrogen peroxide and nitrogen oxide (NO) level after treating with Rd and Rg1 respectively, on the other hand SOD, catalase (CAT) and glutathione (GSH) are maintaining relative high level than pretreat or control group.[74,75] It is because the ginsenosides they used act as antioxidant and scavenge the ROS, or even directly activate those enzyme.

In addition, ginseng is well known as its neuronal protective characteristic, as it have both anti-neurodegeneration and anti-amnestic function.[76,77] Ginsenosides can maintain the cell functioning, increase the survival rate and extent the neurite,[78] also it protects neurons from glutamate-induce neurotoxicity and thus prevent cellular hypoxia.[79] Since glutamate can induce the production of 1-methyl 1-4 phenylpyridinum (MPP^+) which can further trigger cell death in dopamnergic neurons through oxidizing dopamine.[80] It can also inhibit N-methyl-D-aspartate (NMDA) and its related receptor which can prevent over influx of calcium ions into neuron cells and over-stimulation, thus protecting neuron.[81] Some reports claim that ginsenosides, such as Rg1 and Rb1, can increase cholinergic system by increasing the amount of acetylcholine receptor and cAMP which may trigger the production of ATP and also decrease the nitric oxide content, protecting the neuron from alive and providing cognitive and neuron protection effect.[82] Moreover, ginseng carry immune-modulation characteristic. During aging, T-cell function will decline and interleukin-2 (IL-2) level which is essential in immunity will also decrease. Radad *et al* reported that 20mg/kg Rg1 in vivo or 10umol/L Rg1 in vitro can promote lymphocyte proliferation and enhance IL-2 level. [83] At the same time, it can increase cAMP and cGMP, which is the second messenger in many immunity pathway.[84]

There are still many protective functions of ginseng have not been addressed; for examples their anti-cancer, anti-stress effect on cardiovascular system. This explains why it is a commonly used and well known herb in our society.

SUMMARY OF FUNCTION OF ANTI-AGING HERBS

There are still many other types of anti-aging herbs. The above examples are well known and easy-to-find in the market. Different medicinal herbs contain different compounds and carry out different functions by different level and pathway. However, most of them are focused on same target: enhance the cell maintenance, prevent the cell death. Also, it can be

seen that they are working through four major mechanisms: 1) Anti-oxidation and glycosylation, 2) Affecting metabolism through enhance or inhibit, 3) Improve the immune system, 4) Protect neural system.

Anti-oxidation and glycosylation

ROS production is involved in many biochemical pathways, such as phosphorylation and inflammation. It is highly related to pathologic condition, such as cancer, or neural degeneration. In addition, there is anti-oxidative defense in organism body, such as SOD, CAT, GSH. The anti-aging herbs usually work on the balance or improvement of these enzymes, such that can tolerate the oxidation and prevent damage from these free radicals.

Affecting metabolism through enhancing or inhibiting

It can be observed that the three examples described usually work on the energy production of the cell. For example, ginkgo extract can maintain blood circulation by anti-PAF so that high blood pressure can be reduced. Also it protects mitochondrion from damage and hence maintain sufficient ATP formation.[49] The same way is used in ginseng[85] and *Lycium barbarum* [56] through controlling the blood pressure and blood glucose level.

Improve the immune system

Immunity declines with age in many animals. It is usually related to the decline of lymphocyte amount which associated with the presence of corresponding receptor[30] or factors (e.g. IL-2).[26] These medicinal herbs usually up regulate the immunity by activating the production of these key factors. For example, both extracts from ginseng[84] and *Lycium barbarum*[59] will enhance the expression of IL-2 and thus improve the immunity.

Protect neural system

Neural system is the most important part in the body, as it controls lots of homeostasis as well as learning, cognitive or other function. Lots of neuron will be degenerated with age, as damage and energy deprivation occur. Therefore, the anti-aging herbs usually enhance the production of ATP. It works on maintenance of cell function. They usually prevent the cell from death by increasing the Bcl-2 and inhibiting the pro-apoptotic factor such as Bax, caspase family. It also inhibits the factor that will activate apoptotic pathway such as Aβ.[53] Some even promote cell growth, such as ginsenosides which can activate extension of neurite growth.[82]

Life style, supplement food and aging

Though these medicinal herbs can help to extend life span or improve health status. But they also contain toxicity or may be harmful when overdose. For examples, ginkgo can promote health circulatory system through anti-PAF, however, it will lead to serious bleeding when inhibiting blood clotting if it is in excess.[33] In order to maintain health with age, life style is important. It is obvious that obesity will lead to accumulation of ROS, as lipid in the tissue may easily be oxidized. Irregular resting also accelerates aging, since stress may increase formation of free radical and cause overload of brain.

CONCLUSION

Aging mechanism is a complicated system in the body. Since the life span of the population over the world is increasing, aging-related problems should be noticed. In addition, some medicinal herbs are effective in anti-aging. They may work on different pathway, but come with the same principle, include maintain sufficient energy production, lower the ROS level, enhance the immunity and neuronal protection. It is also important to maintain a healthy life style in order to retard aging.

Author's background

Mr TSANG Kwok *Hong holds a BSc degree in Chemistry. He was an undergraduate student in the Department of Biology and Chemistry, City University of Hong Kong before 2012. This is a piece of his final year literature project working under Dr HY Cheung's supervision.* ***Dr. CHEUNG Hon-Yeung****, who is an associate professor of Pharmaceutical Microbiology & Biotechnology at the City University of Hong Kong since 1989, is a manufacturing pharmacist and biotechnologist. He has more than 40 years of work experiences in industries, academic and consultancy jobs. He was an expert witness in court and a member of the Biotechnology Committee for Hong Kong and Shenzhen Government. Dr. Cheung has published more than 220 papers and articles in many prestigious international journals. His email address: bhhonyun@cityu.edu.cn.hk*

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Study Visit to Beijing and the Forbidden City International Pharmacist Forum 2014

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On 15 May 2014, the Pharmaceutical Society of Hong Kong (PSHK), led by Ms. Mary Cheng, President of the Pharmaceutical Society of Hong Kong, formed a delegation of 9 pharmacists and 17 students attended the Forbidden City International Pharmacist Forum in Beijing. This year, there were 5 speakers attending the Forum, namely Prof. Larry Baum, Ms. Chiang Sau Chu, Mr. Philip Kwok, Ms. Ritchie Kwok and Prof. Vivian Lee. Ms. Mary Catherine Cheng and Mr. Benjamin Kwong were moderators for several sessions. Since 2011, PSHK has sponsored pharmacy students partially to attend the conference to broaden their vision on different pharmaceutical fields outside Hong Kong. Whenever possible, PSHK would arrange visits to hospitals and industry in Beijing. The delegation arrived Beijing in the evening of 15 May 2014 and were driven to the Conference venue, at Jiu Hua Resort and Convention Centre.

The delegation departs at the HK International Airport

Ms. Ritchie Kwok as speaker

VISIT TO JOINTOWN PHARMACEUTICAL GROUP (九洲通医药集团)

In the morning of 16 May 2014, we visited Jointown Pharmaceutical Group, a Pharmaceutical Logistic Center which delivers medicines all over China. We were met by Mr. Shulin Liu, Vice President and Dr. Kevin Gu, the Chief Technical Officer and Mr. Zhiyong Gao, Vice President who show us around the Centre. It was an eye opening opportunity to visit its headquarters and warehouse to learn about the management system of drug storage, picking, packing and delivery. We found that there are many regulations or notice boards to remind them about the safety issues. Barcode system is also adopted to avoid mistakes during the drug picking step. Their delivery system is so advanced such that they deal with the orders from different regions within 24 hours.

Jointown Pharmaceutical Group is not only a distributor of pharmaceutical products; it also provides services that help their customers to design and build suitable storage environment for pharmaceutical products. The representative of the group reflected to us that the storage of pharmaceutical products is poorly managed in many hospitals in the mainland, especially in the less developed cities; they discovered in a visit that the stock in the warehouse of a hospital in a rural area had already expired for three years. Moreover the pharmacists in local hospitals are usually busy dealing with the stock management at the expense of the precious time that can be used in providing other pharmaceutical care services. The vision of the group is to distribute the pharmaceutical products to their respective destination—the shelves in the pharmacy, instead of transporting the pharmaceutical products to the warehouse only. In this way the pharmacists in local hospital pharmacies are more able to engage in other services. This is a novel concept which we are not aware of previously.

Conveyer belt at Jointown

Visit at Jointown

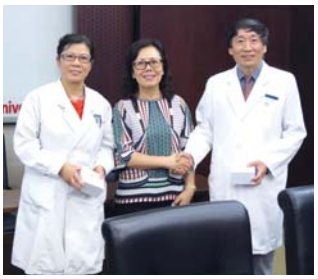
Storage rack at Jointown

VISIT TO BEIJING FEIENDSHIP HOSPITAL

After visiting Jointown Pharmaceutical Group Co. Ltd, we set off to our next destination, Beijing Friendship Hospital which is affiliated to the Capital Medical University. It is comparably hectic as in the Hong Kong public hospitals.

The pharmacist in charge, Ms. Shen Su first led us to the in-patient pharmacy. The settings are quite similar to that in Hong Kong. A unique feature is the storage and use of Chinese proprietary medicines in Beijing hospitals. The pharmacists also introduced their latest technology and equipment to us. For example, the automated inventory and dispensing control system which aims to reduce dispensing errors and enhance the efficiency of stock storing and dispensing so that pharmacists can contribute more to clinical work. However, the down side of this system is that only package of a certain size can be placed in the machine. Therefore, it is not universal for all of the medications. In fact, similar systems can be found in The Hong Kong University of Science & Technology and the Prince of Wales Hospital. In addition, similar to many Hong Kong hospitals, for safer use of drugs, especially the elderly and chronically ill patients who need to take multiple drugs, a multi-drug unit dose dispensing system is established in Friendship Hospital. The pharmacists explain the current situation and outlook of Beijing pharmaceutical industry. They also face the problem of manpower shortage, with increased workload for pharmacists.

We were given a presentation on the Beijing Friendship Hospital by Prof. Zhang Jian, Professor, Chief physician and Vice President of the Beijing Friendship Hospital. The discussions between the pharmacists from Hong Kong and the Hospital are beneficial to us all. The integration of Western and Chinese medicine is advocated in the hospital and it is also one of Hong Kong's future development trends. Finally, we thank Prof. Zhang Jian and Ms. Shen Su and the Friendship Hospital Pharmacists for their reception and departed in the late afternoon.



Ms. Shen Su, Ms. Mary Cheng, Prof. Zhang Jian at Beijing Friedship Hospital

Group photo at Beijing Friendship Hospital

THE FORBIDDEN CITY INTERNATIONAL PHARMACIST FORUM 2014

The Forbidden City International Pharmacist Forum 2014(FCPF) from 16-18th May 2014 was organized by the China Health Promotion Foundation together with China Pharmaceutical Association, 日本病院药剂师会，中日医学科技交流协会，药品评价杂志社 and American Society of Health System Pharmacists The theme of the 2014 Forum was "Promoting Rational Drug Use – You are the Power". The Forum invited local and overseas pharmacists to participate by sharing and discussing successful experiences, inspirations and new initiatives in 15 special sessions, including Pharmacy Administration, Chronic Disease Management and Rational Drug Use, Reevaluation of listed drugs, Medical Insurance Policy, Pharmacists and Rational Drug Use, and 4 competitions such as Young Pharmacists Debate Competitions, Popular Science Star of Rational Drug Use Speech Competition.

Some of the leaders from China, USA, Japan, including Hong Kong were presented a special token of appreciation in support of the FCPF.

Leaders receiving token of appreciation for support of FC.PF

For the Gala Dinner on 16 May 2014, participants from different countries and regions gave a performance. We sang two songs and looked awesome on stage with our red colour T-shirts.

PSHK Gala dinner performance

Students attending the Forum

Mary Cheng, Vivian Lee, Chiang Sau Chu, Benjamin Kwong, Larry Baum, Philip Kwok & Ritchie Kwok

Benjamin Kwong as moderator

Promoting Rational Use of Drugs – You are the Power (Forum Theme Reflection)

In the FIP Centennial congress in Amsterdam 2012, the IMS Institute for Health Informatics issued a report which estimated an opportunity to save a half trillion dollars in annual global health expenditure through rational use of medicines. Do we still want to keep wasting one of the most precious resource for human beings, the resource which can cure diseases, improving well-being and saving lives: Medicines?

The reasons leading to this guilty aberration: over use / misuse / underuse of medications include inappropriate use of antimicrobials, failure to prescribe in accordance with clinical guidelines, non-adherence, inappropriate self-medication, inadequate training and lack of information.

Being pharmacy students, we are trained to be the professionals equipped with the best knowledge and capacity for rational and quality drug use. Therefore, pharmacists should play a proactive and central role in rational drug use through different levels.

First, provide direct improvements on the use of medications at patient level. These include the provision of clinical pharmacy services, drug information, advice and recommendations to patients and other healthcare providers.

Second, assure there are safety systems for the use of drugs. These include development and maintenance of medication safety plans and strategies, effective monitoring systems and provision of established best practices and guidelines.

TDM, Genomics and Individualized Medicines

Clinical safety and rational use of drugs inevitably require therapeutic drug monitoring (TDM). Owing to variability in pharmacokinetic performance and pharmacodynamics, numerous challenges have to be overcome to achieve individualized medicine. Thus, studies in diverse fields such as pharmacogenomics (PGx) and quality control system have been done to enhance the safety and accuracy of TDM.

A number of drugs were discussed in the field of TDM. Tacrolimus, an immunosuppressive drug after solid organ transplantation, has especially received attention due to its extensive use. Its PGx, dose adjustment based on gene variation and pharmacokinetics of its extended – release capsule (Prograf) were studied. Some TDM practices related to PGx in Hong Kong were also reviewed. Though PGx plays a role in TDM, it is currently underutilized. A speaker from Nanjing University suggested some major obstacles to implementing gene – guided personalized medicine but he insisted that PGx would be a new medication model and we should overcome these challenges, instead of abandoning the use of PGx.

Apart from PGx, the role of pharmacist intervention is also important in TDM. A professor from Kyunghee University in Korea evaluated the effectiveness of “Heparin Order & Administration Program” (HOAP) in reducing incidence of medication error. The contribution of pharmacists in TDM to date is unquestionable. Yet, excellence is a continuous work and PGx would probably be one of the potential breakthroughs.

Youth Pharmacist Debate Competition

On the afternoon of the first day of the conference, we appreciated three debates on different topics regarding the practice of pharmacy in China. The competitors were young hospital pharmacists from various provinces in mainland China. Although young in age, all of them were well-prepared and experienced enough to present us an in-depth as well as comprehensive view regarding the controversial areas in pharmacy practice and have inspired our own thoughts on the role of pharmacist under the special Chinese background, as a service provider and pharmacy manager.

Topic 1: The Pro and Cons of Integrating Outpatient TCM and Western Pharmacy

The principle of integrating outpatient TCM and Western pharmacy is picking up both TCM and western medicine in one pharmacy instead of separate pharmacy. The affirmative side claimed that this is a more convenient way for the patients to obtain the medications as they can get both TCM and western medicine in one location, which can enhance patient satisfaction towards the pharmacy services by reducing the waiting time.

On the other hand, the negative side argued that the medication safety would be a major concern after integration. The prescription containing both TCM and western medicine can have a higher chance of leading to medication errors when the picking process for both TCM and Western medicine is taken place in the same pharmacy.

Topic 2: Should the Pharmacist be Empowered with Prescription Rights in China?

The affirmative side claimed that the pharmacist authorized with prescribing rights can improve the management of chronic diseases by picking the most appropriate medication for the patients. As a result, this can enhance the medication safety and reduce the cost of medical care due to the effective use of drug therapy.

The argument of the negative side is related to the role conflicts between the physician and the pharmacist. Physician and pharmacist show their own professions respectively. Physician focuses on diagnosis and writing prescription while pharmacist verifies the prescriptions. The empowerment of the pharmacist with prescription rights is still not applicable since the prescribing practice of the pharmacist is not mature in

China. Hence a clearer role differentiation is a major challenge for this implementation.

Topic 3: Should the Pharmacists Take more Responsibility in Patient Harm Caused by Irrational Medication Use?

The affirmative side claimed that the major duty of pharmacist is to verify the prescription given by the physicians and perform therapeutic monitoring to promote rational drug use. Therefore pharmacists should share the responsibility with the doctor to ensure patient safety.

On the other hand, the negative side argued that the physicians should have a greater responsibility for the whole treatment as they make diagnosis and deliver prescription through different scanning and lab results and they are the only one who can confirm the medical status of the patient.

After the three exciting competitions, we were not only impressed by the delicate logic and debate skills of the youth pharmacist competitors, but were also inspired by them and developed our own thoughts. Firstly, with the history and prevalence of using traditional Chinese medicines, we as pharmacists practicing in China should be familiar and masters at not only western but also Chinese medicines. Secondly, pharmacists as the experts in medication are deemed to take on more responsibility in the management of medication regimens as well as chronic diseases. However this is only to be fulfilled with the complement and fully establishment of relevant regulations. Last but not the least, pharmacists as the safety guards of medication usage should be more alerted and responsible as we are endowed with more power.

The Role of Pharmacists in Geriatrics

Geriatrics is a very big topic in health care system. Senior patients would easily have several diseases at the same time, hence they may need to take different types of medicines to target various diseases. Therefore, they are prone to suffer from the drug-drug interactions or adverse effects from polypharmacy.

As a pharmacist, we play a vital role to use the drugs correctly in order to improve the quality of life of the elderly. For example, pharmacists need to pay extra attention when they are in the geriatric ward, they need to assess the medication of each new patient carefully to find out if there exists any ADRs or risk of polypharmacy. Moreover, the whole geriatric team needs to cooperate to meet the team members to deal with the medication problems encountered. Education is also another crucial step to manage the geriatrics problems, pharmacists must be proactive to understand the worries of the elderly and help solve those questions, as well as teaching them how to use the drugs appropriately. In around 2040, around 30% of Hong Kong population would be 65 years old or above. It seems that geriatrics would be a hot topic in the future, so I think a more in-depth study in geriatrics should be done in the future.

The combined use of traditional Chinese medicine (TCM) and western medicine to treat diseases

It is very common to use TCM in combination with western medicine to treat diseases in China. According to Prof. Xu DeSheng, a speaker from Shanghai Shuguang Hospital, TCM mainly focus on the integrity of human body but is not well-targeted to a specific disease; while western medicine is well-targeted but with relatively more side-effects. Thus, combination regimen is mutually complementary in improving therapeutic effects, reducing adverse effects, and lowering the total medical expenditure. For example, co-administration of Schizandra chinensis (五味子) with cyclosporine can reduce the dose of cyclosporine in immunosuppression therapy, which saves money for the patient (due to the high cost of the cyclosporine) and achieves better therapeutic outcome.

However, in some cases, combination therapy may have certain drug-drug interactions, causing significant adverse effects and leading to patient's death. To prevent this situation, it is necessary to master the pharmacokinetic and pharmacodynamics of both TCM and western medicine to make sure the combination therapy is effective without causing severe side effects to the patients. Some important pharmacokinetic and pharmacodynamics considerations include: Is there any CYP450 enzyme induced or inhibited by the TCM which may alter the serum level of the western drug? Will the therapeutic effect be enhanced or diminished by the TCM? Is there any physical incompatibility or chemical interaction when the TCM and western medicine are taking at the same time? Finally, the speaker also addressed that, as the therapeutic effect of the combined use of both medicines is becoming better recognized, their clinical use is becoming more and more popular. Thus, the role of pharmacists are becoming more important in designing patient-specific drug-regimen and therapeutic drug monitoring, in order to optimize therapeutic outcome and minimize any potential adverse effects.

Clinical pathway

After all these lectures, my understanding towards clinical pathway is rewarding. A correct clinical pathway could reduce the burden of both doctors and patients in hospitals which they are facing heavy workloads every day. Treatment using fluid is very common in clinical pathways, in one lecture, the lecturer clearly explained that parental nutrition might not be helpful to every patient; instead, if it was used upon patients who have no risk of nutrition imbalance, the application of the needles needed to carry out parental nutrition would only increase the risk of microbial infection. Another lecturer also clearly explained the different components inside various fluids and important points to notice when we were using them. Some hospitals even upgraded their clinical pathway practice to a computerized one in which less medical errors and unsuitable medicinal prescription could be achieved.

Particular specialty wards, such as nephrology, would benefit a lot if a good clinical pathway is implemented as nephrology patients would need to use glucocorticoids frequently. In addition to that, they are also bound to chronic treatment and a lot of concomitant drugs. Pharmacists should bear the responsibility to set up a sequence of clinical pathway to ensure patients could receive the best treatment. However in China today, a concrete working system regarding these issues is still not established, therefore we, the future pharmacists, should also think about how we could contribute to this project and together with other important components of a good medical team, such as the doctors and the supportive staffs , we could make a better future.

Clinical Pharmacists Practice Case Show in Antineoplastic Therapy

"Clinical Pharmacists Practice Case Show in Antineoplastic Therapy" was successfully held in the afternoon on May 17, with a total of 9 speakers who are current clinical pharmacists in their own provinces.

Each speaker is asked to present his/her case study report, including the analysis and practice plan within 15 minutes. And the judges, who are senior pharmacists, will rate their performance based on their presentation skill and content. And the one with the highest score wins the competition.

The competition was quite interesting and easy to follow. Firstly, a brief summary of the case they are going to present, showing patients symptoms and background, with some medical and medication information, followed by some lab assessment results. Then they present their analysis and some feasible purposed plans. And come out with what they think the most suitable plan by comparison.

The way these 9 speakers present on stage was very impressive. Not only do they present in a very clear, organized manner, but also with confidence and willingness to share their ideas by explaining in details on how they choose the most suitable plan for the patients, and not by saying "because it is commonly used in the hospital"

One of the speakers even made a schedule, describing how the patient behaves throughout the medication treatment. It was quite enjoyable listening to her presentation

CONCLUSION

The visit to Jointown Pharmaceutical Group enables us to understand the operation of a Logistic Company in China. The visit to Beijing Friendship Hospital makes us realized that hospitals in China are extremely busy and are using a lot of automation to help them in the process of delivering drugs to patients. The Forbidden City Forum has attracted many speakers from all over the world and has become a good training ground for young pharmacists in China as well as a platform to meet reputable speakers from all over the world.

The Society of Hospital Pharmacists (SHPHK) Office Bearers and Subject Officers 2014-2015

Appointment of Office Bearers and Subject Officers

President	CHUI Chun Ming William
Vice President	CHAN Wing Lam Phoebe
Secretary	CHU Man Wa Amy
Treasurer	LAI Oi Lun Ellen

Subject Officer

Member Relations	LING Ho Ming Michael
Clinical Forum	CHAN Wing Lam Phoebe HUI Hoi Yun Helen KWOK Ching Chi Ritchie
Publication & Pharmaceutical Journal	KWOK Ching Chi Ritchie WONG Sze Ho Johnny WONG Kai Chung Vincent
Pharmaceutical Journal Membership	CHAU Yiu Hong Raymond
PCCC	CHUNG Wing Fai Kenneth
IT	NG Man Keung
DERC Director Associate Directors	 CHIANG Sau Chu LAM Po Yu Daisy SO Yiu Wah

The 43rd Term Practising Pharmacists Association of Hong Kong (PPAHK) General Council, 2014 – 2015

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TRAJENTA® DUO
(Boehringer Ingelheim)
(Eli Lilly)

Edited by Ms. Ivy Chan

Active Ingredient:
Linagliptin and Metformin Hydrochloride

Presentation:
Trajenta Duo 2.5mg/500mg - Each film-coated tablet contains 2.5 mg of linagliptin and 500mg of metformin hydrochloride

Trajenta Duo 2.5mg/850mg - Each film-coated tablet contains 2.5 mg of linagliptin and 850mg of metformin hydrochloride

Trajenta Duo 2.5mg/1000mg - Each film-coated tablet contains 2.5 mg of linagliptin and 1000mg of metformin hydrochloride

Pharmacological Properties:
Linagliptin is an inhibitor of the enzyme DPP-4 (Dipeptidyl peptidase 4) an enzyme which is involved in the inactivation of the incretin hormones GLP-1 and GIP (glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide). These hormones are rapidly degraded by the enzyme DPP-4. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretins are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. Furthermore GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output. Linagliptin binds very effectively to DPP-4 in a reversible manner and thus leads to a sustained increase and a prolongation of active incretin levels. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion thus resulting in an overall improvement in the glucose homoeostasis. Linagliptin binds selectively to DPP-4 and exhibits a > 10,000 fold selectivity versus DPP-8 or DPP-9 activity *in vitro*.

Metformin hydrochloride is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin hydrochloride may act via 3 mechanisms:
(1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis,
(2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization,
(3) and delay of intestinal glucose absorption.
Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase.
Metformin hydrochloride increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.

In humans, independently of its action on glycaemia, metformin hydrochloride has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin hydrochloride reduces total cholesterol, LDL cholesterol and triglyceride levels.

Indications:
Treatment of adult patients with type 2 diabetes mellitus:
Trajenta Duo is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients inadequately controlled on their maximal tolerated dose of metformin alone, or those already being treated with the combination of linagliptin and metformin.
Trajenta Duo is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.

Dosage and Administration:
The dose of antihyperglycaemic therapy with Trajenta Duo should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability, while not exceeding the maximum recommended daily dose of 5 mg linagliptin plus 2,000 mg of metformin hydrochloride.
Trajenta Duo should be taken twice daily with meals.

Contraindications:
Hypersensitivity to the active substance or to any of the excipients
Diabetic ketoacidosis, diabetic pre-coma.
Renal failure or renal dysfunction (creatinine clearance < 60 ml/min).
Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock.
Acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, recent myocardial infarction, shock.
Hepatic impairment, acute alcohol intoxication, alcoholism.

Precautions:
Trajenta Duo should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
When linagliptin was added to a sulphonylurea on a background of metformin, the incidence of hypoglycaemia was increased over that of placebo.
Sulphonylureas are known to cause hypoglycaemia. Therefore, caution is advised when Trajenta Duo is used in combination with a sulphonylurea. A dose reduction of the sulphonylurea may be considered.

Drug Interactions:

<u>Linagliptin</u>
Linagliptin is a weak competitive and a weak to moderate mechanism-based inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes. It is not an inducer of CYP isozymes.
Linagliptin is a P-glycoprotein substrate, and inhibits P-glycoprotein mediated transport of digoxin with low potency. Based on these results and *in vivo* interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates.
Clinical data suggest that the risk for clinically meaningful interactions by co-administered medicinal products is low.

Metformin
The following combination requires precautions for use:
Glucocorticoids (given by systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicinal products. If necessary, the dose of the anti-hyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

Combinations not recommended:
There is increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic impairment due to the metformin active substance. Consumption of alcohol and medicinal products containing alcohol should be avoided.

Cationic substances that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with metformin by competing for common renal tubular transport systems.

The intravascular administration of iodinated contrast agents in radiological studies may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. Therefore, Trajenta Duo must be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Side Effects:
The most frequently reported adverse reaction was diarrhoea, hypoglycaemia may occur when Trajenta Duo is administered together with sulphonylurea.

Forensic Classification:
P1S1S3

ZALTRAP™ 25 mg/ml
(SANOFI)

Prepared by Raymond Wong, 2nd year Pharmacy student, The University of Hong Kong, and edited by Lucilla Leung

Active Ingredient:
Aflibercept

Presentation:
One ml of concentrate for solution for infusion contains 25 mg aflibercept*.
One vial of 4 ml of concentrate contains 100 mg of aflibercept.
One vial of 8 ml of concentrate contains 200 mg of aflibercept.
*Aflibercept is produced in a Chinese hamster ovary (CHO) K-1 mammalian expression system by recombinant DNA technology.
Concentrate for solution for infusion (sterile concentrate). The concentrate is a clear colourless to pale yellow solution.

Pharmacological Properties:
Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: not yet assigned

Mechanism of Action:
Vascular endothelial growth factor A and B (VEGF-A, VEGF-B), and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF-A acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF and VEGF-B bind only to VEGFR-1, which is also present on the surface of leukocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PlGF is also linked to pathological neovascularisation and recruitment of inflammatory cells into tumours.

Aflibercept, also known as VEGF TRAP in the scientific literature, is a recombinant fusion protein consisting of VEGF-binding portions from the extracellular domains of human VEGF receptors 1 and 2 fused to the Fc portion of the human IgG1. Aflibercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) K-1 mammalian expression system. Aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa.

Aflibercept acts as a soluble decoy receptor that binds to VEGF-A, with higher affinity than its native receptors, as well as the related ligands PlGF and VEGF-B. By acting as a ligand trap, aflibercept prevents binding of endogenous ligands to their cognate receptors and thereby blocks receptor mediated signalling.

Aflibercept blocks the activation of VEGF receptors and the proliferation of endothelial cells, thereby inhibiting the growth of new vessels that supply tumours with oxygen and nutrients.

Aflibercept binds to human VEGF-A (equilibrium dissociation constant KD of 0.5 pM for VEGF-A165 and 0.36 pM for VEGF-A121), to human PlGF (KD of 39 pM for PlGF-2), and to human VEGF-B (KD of 1.92 pM) to form a stable, inert complex which has no detectable biological activity.

Indications:
ZALTRAP in combination with irinotecan/ 5-fluorouracil/ folinic acid (FOLFIRI) chemotherapy is indicated in adults with metastatic colorectal cancer (MCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen.

DOSAGE AND ADMINISTRATION:
ZALTRAP should be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products.

Dosage
The recommended dose of ZALTRAP, administered as an intravenous infusion over 1 hour, is 4 mg/kg of body weight, followed by the FOLFIRI regimen. This is considered as one treatment cycle.

The FOLFIRI regimen to be used is irinotecan 180mg/m2 intravenous infusion over 90 minutes and folinic acid (dl racemic) 400 mg/m2 intravenous infusion over 2 hours at the same time on day 1 using a Y-line, followed by 5-fluorouracil (5-FU) 400 mg/m2 intravenous bolus, followed by 5-FU 2400 mg/m2 continuous intravenous infusion over 46 hours.

The treatment cycle is repeated every 2 weeks.

ZALTRAP treatment should be continued until disease progression or unacceptable toxicity occurs.

Administration
ZALTRAP is to be administered only as an intravenous infusion over 1hour. Due to hyperosmolality (1000 mOsmol/kg) of the ZALTRAP concentrate, undiluted ZALTRAP concentrate must not be administered as an intravenous push or bolus. ZALTRAP must not be administered as an intravitreal injection. Each vial of concentrate for solution for infusion is for single use (single-dose) only.
Diluted solutions of ZALTRAP should be administered using infusion sets containing a 0.2 micron polyethersulfone filter.
The infusion sets should be made of one of the following materials:
- polyvinyl chloride (PVC) containing bis(2-ethylhexyl) phthalate (DEHP)
- DEHP free PVC containing trioctyl-trimellitate (TOTM)
- polypropylene
- polyethylene lined PVC
- polyurethane

Filters made of polyvinylidene fluoride (PVDF) or nylon must not be used.

Contraindications:
Hypersensitivity to aflibercept or to any of the excipients
Ophthalmic / intravitreal use due to hyperosmotic properties of ZALTRAP
For contraindications related to FOLFIRI components (irinotecan, 5-FU, and folinic acid), refer to the current respective summary of product characteristics.

Precautions:
Haemorrhage
An increased risk of haemorrhage, including severe and sometimes fatal haemorrhagic events has been reported in patients treated with aflibercept.
Patients should be monitored for signs and symptoms of GI bleeding and other severe bleeding. Aflibercept should not be administered to patients with severe haemorrhage.

Thrombocytopenia has been reported in patients treated with the ZALTRAP/FOLFIRI regimen. Monitoring of complete blood count (CBC) with platelets is recommended at baseline, prior to initiation of each cycle of aflibercept, and as clinically necessary. Administration of the ZALTRAP/FOLFIRI should be delayed until platelet count is ≥75 × 109/L.

Hypertension
An increased risk of grade 3-4 hypertension (including hypertension and one case of essential hypertension) has been observed in patients treated with the ZALTRAP/FOLFIRI regimen.
Pre-existing hypertension must be adequately controlled before starting aflibercept. If hypertension cannot be adequately controlled, treatment with aflibercept should not be initiated. It is recommended to monitor blood pressure every two weeks, including before each administration or as clinically indicated during treatment with aflibercept. In the event of hypertension on aflibercept treatment, blood pressure should be controlled with appropriate anti-hypertensive therapy and blood pressure should be monitored regularly. In case of severe hypertension, the treatment should be suspended until controlled and the aflibercept dose should be reduced to 2 mg/kg for subsequent cycles. Aflibercept should be permanently discontinued if hypertension cannot be adequately managed with appropriate anti-hypertensive therapy, or if hypertensive crisis or hypertensive encephalopathy occurs.

Hypertension may exacerbate underlying cardiovascular disease. Caution should be exercised when treating patients with history of clinically significant cardiovascular disease such as coronary artery disease, or congestive heart failure with ZALTRAP. Patients with NYHA class III or IV congestive heart failure should not be treated with ZALTRAP.

Proteinuria
Severe proteinuria, nephrotic syndrome, and thrombotic microangiopathy (TMA) have been observed in patients treated with aflibercept.
Proteinuria should be monitored by urine dipstick analysis and urinary protein creatinine ratio (UPCR) for the development or worsening of proteinuria before each aflibercept administration. Patients with a UPCR >1 should undergo a 24-hour urine collection.
Aflibercept administration should be suspended for ≥2 grams of proteinuria/ 24 hours and restarted when proteinuria is <2 grams/ 24 hours. If there is recurrence, the administration should be suspended until <2 grams / 24 hours and then the dose reduced to 2 mg/kg. Aflibercept treatment should be discontinued in patients who develop nephrotic syndrome or TMA.

Drug Interactions:
Population pharmacokinetics analysis and inter study comparisons did not reveal any pharmacokinetic drug-drug interaction between aflibercept and the FOLFIRI regimen.

Side Effects:
Summary of the safety profile
The safety of ZALTRAP in combination with FOLFIRI was evaluated in 1216 patients previously treated for metastatic colorectal cancer, of which 611 patients were treated with ZALTRAP 4 mg/kg every two weeks (one cycle) and 605 patients were treated with placebo/FOLFIRI in a phase III study. Patients received a median number of 9 cycles of the ZALTRAP/FOLFIRI regimen.

The most common adverse reactions (all grades, ≥20% incidence) reported at least 2% greater incidence for the ZALTRAP/FOLFIRI regimen as compared to the placebo/FOLFIRI regimen in order of decreasing frequency were leucopenia, diarrhoea, neutropenia, proteinuria, increased aspartate aminotransferase (AST), stomatitis, fatigue, thrombocytopenia, increased alanine aminotransferase (ALT), hypertension, weight loss, decreased appetite, epistaxis, abdominal pain, dysphonia, increased serum creatinine, and headache.

The most common reported grades 3-4 reactions (≥5% incidence) reported at least 2% greater incidence for the ZALTRAP/FOLFIRI regimen as compared to the placebo/FOLFIRI regimen in order of decreasing frequency, were neutropenia, diarrhoea, hypertension, leucopenia, stomatitis, fatigue, proteinuria, and asthenia.

The most frequent adverse reactions leading to permanent discontinuation in ≥1% of patients treated with the ZALTRAP/FOLFIRI regimen were vascular disorders (3.8%) including hypertension (2.3%), infections (3.4%), asthenia/ fatigue (1.6%, 2.1%), diarrhea (2.3%), dehydration (1%), stomatitis (1.1%), neutropenia (1.1%), proteinuria (1.5%), and pulmonary embolism (1.1%).

Forensic Classification:
P1S1S3

長效紓緩關節痛
每天輕鬆第一步

給您關懷的力量

8小時長效紓緩

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近90%受訪醫生推薦*

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